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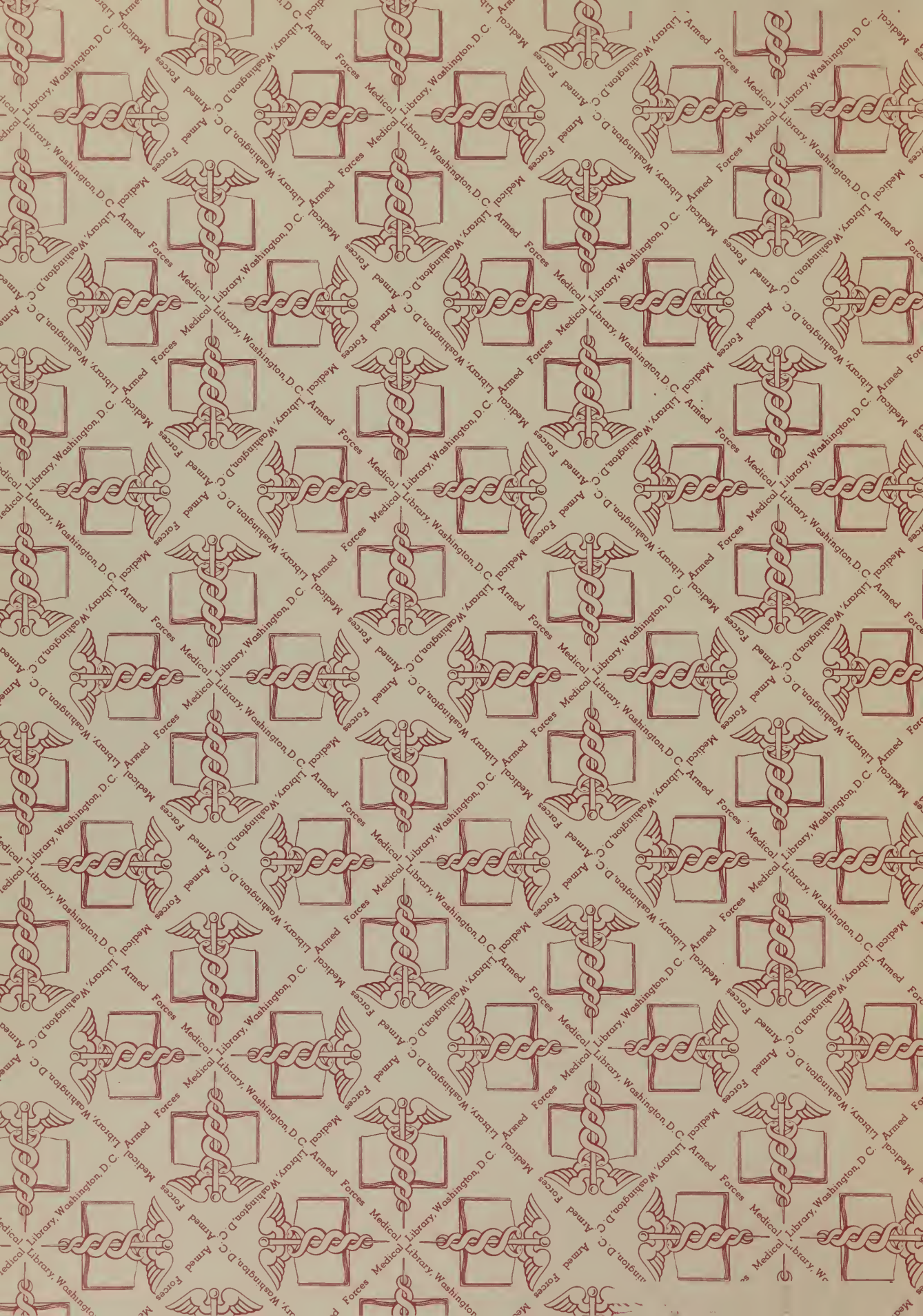
EPIDEMIC HEMORRHAGIC FEVER

by

Claudius F. Mayer, M. D.

Washington, D. C.
December 1951

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P R E F A C E

The Far-Eastern type of epidemic hemorrhagic fever, or infectious hemorrhagic nephroso-nephritis, is a new encounter to the physicians of the Western World and a new challenge to military medical research in the United States.

Russian and Japanese medical people have been studying the disease since the early thirties and their findings also reported in many scattered papers, written in their native languages and printed in various publications that are now difficult to obtain and hard to read.

My monograph on Epidemic Hemorrhagic Fever brings together the scattered data recorded in these foreign publications and coordinates the results of about fifteen years of investigation carried out by the two nations that opposed each other in the 'cockpit of Asia' (ROBERTSON; 80)

Since information on the subject is in urgent demand I did not wish to withhold the publication of this paper until mid-January while preparing its final form. Hence, this 'preliminary draft' is issued to satisfy the immediate needs of research workers and others. Certain parts have been omitted from the text, but they will be included in the final edition, together with an annotated list of the literature.

I am grateful to a number of people whose splendid cooperation, information, advice, technical skill and willingness helped my own efforts to the speedy realization of this individual project.

My thanks are due especially to the following:

Drs. K. F. MOSTOFI, Armed Forces Institute of Pathology, and C. H. BINFORD, USPHS, who brought the problem to my attention in early October; Dr. JOHNSON, U. S. National Museum, who advised me on Apodemus and Laelaps; Miss K. MERRILL, Mr. and Mrs T. TAKASHITA and Mrs. Regina PLAVSKY for their contribution and help in the preliminary preparation of the material; Maj. Gen. Edgar E. HUME, U. S. Army, whose continued interest stimulated me in my work.

The printing of this publication was made possible by Lt. Col. F. B. ROGERS, M. C.

The speedy publication of the paper, from the 4th to the 7th of December, depended entirely upon the unexcelled teamwork and enthusiasm of the following persons: Dr. Isabelle ENTRIKIN, who, besides acting as editor, was the chief typesetter, together with Mr. Harold KOEHLER and Mr. Edward MILLER. The multiplication of the illustrations was made by Mr. R. H. ECKINBACH and his staff, especially Mrs. N. MARKHAM and Mrs. CORRIGAN. Technical help was also given by Mrs. S. WINECOFF and the Misses C. HILBRANDT, S. BROWN, H. BISHOP and G. TURNER. Mr. Patrick PATTERSON was the skillful mimeographer.

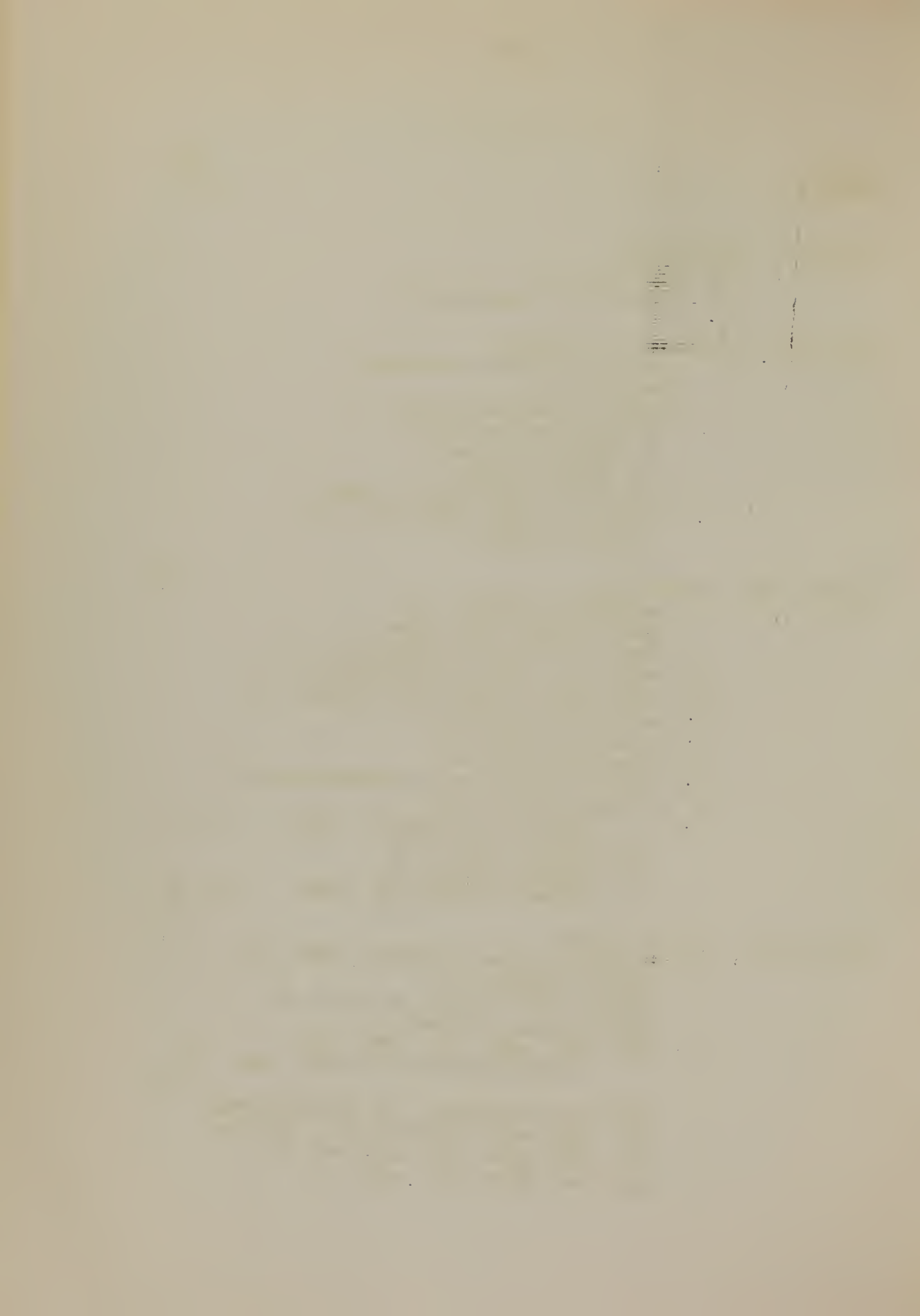
If this paper helps military medical research in finding a quick shortcut to the mastery of the disease, to the safe recovery of the afflicted and to the prevention of new outbreaks, then we feel that our efforts have not been in vain.

7 December 1951
Washington, D. C.

Claudius F. MAYER, M. D.

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EHF: Epidemic hemorrhagic fever

EPIDEMIC HEMORRHAGIC FEVER

A collective study of the literature on
the Far-Eastern type of the disease

By CLAUDIUS F. MAYER, M. D.

Chief of Division; the Editor of the
Index-Catalogue of the
Library of the Surgeon-General's Office

CHAPTER I

INTRODUCTION

During the last two decades there have been various outbreaks of mystifying epidemics reported from different regions of the vast Eurasian Soviet Union and its neighboring countries. The outbreaks occurred roughly within the huge segment of the globe between the 35th and 55th latitudes North, and all have appeared under the common mask of high fever with hemorrhagic diathesis. Hence, many of them were called 'Epidemic hemorrhagic fever' either by the Russians or by their neighbors.

Within the geographic area indicated above, varieties of epidemic hemorrhagic fever (EHF in the rest of the paper) occurred chiefly at four endemic centers: 1) in Bukovina, 2) in the Crimean District, 3) in the Omsk-Tashkent-Stalinabad sector, and 4) in the Far-East, in the Manchuria-Primorskaya-Korea triangle.

This paper deals primarily with the EHF endemic in the Far-East.

*
* *

News dispatches of the Associated Press and United Press carried to the public the disturbing announcement of the existence of a 'strange Oriental disease', a 'mystery disease' which has affected U.N. troops in Korea. It was hinted that it might be identical with the same epidemic hemorrhagic fever that had afflicted Japanese troops which were stationed in Manchuria before World War II (22; 21; 20; 18).

The headlines of daily papers shouted that the mysterious virus had already infected a young research worker in Pittsburgh who attempted to seek a cure for the malady. It was also asserted that the virus paralyzed him, and air had to be "pumped into his lungs through a hole cut in his neck" (Washington Post, Nov. 10, 1951).

The disease is neither as mysterious, nor as strange as the papers have made it. For more than 15 years it has been studied not only by the Japanese but also by the Russians, and the military pathologists and virologists of both nations have written many papers on the outbreaks of the disease endemic in the provinces on both sides of the lower Amur where southeast Asiatic Russia, Manchuria, and Korea meet in the Far East.

It is my purpose to collect in this paper the available Russian and Japanese literature on the Far Eastern type of epidemic hemorrhagic fever, in the form of a comprehensive review, with some attempt at synthesis of the various findings into a complete picture of the subject matter, for the benefit of our fighting troops and the medical men who are now devoting their energy to the mastery of the 'mystery disease'.

Previous to this paper there was in existence a mimeographed report in English, prepared in February 1951 by Capt. John P. CRAIG, of the 406th Medical General Laboratory. It was quoted in the 12-leaf hectographed pamphlet compiled by Capt. Ralph M. TAKAMI, medical intelligence officer in the U. S. Army in Korea, and issued 13 August, 1951. This pamphlet, which I received recently (29 Nov. 1951), is based upon the review of eight Japanese articles written in 1943 and 1944 on EHF but no later Japanese and no Russian literature was mentioned in it.

1. Definition.

Epidemic hemorrhagic fever is an acute, infectious disease of man and possibly of animals (horse, cat), of 3 to 4 weeks duration, caused by an unknown pathogenic agent, most likely a virus. It is endemic in large portions of Eastern and Northern Manchuria, the Primorskaya of Siberia, and perhaps Korea, where -- along the rivers-- it occurs in small epidemics spread by parasitic mites of rodents. It is characterized by a typical short fever, a peculiar flushed aspect of the face, hemorrhagic purpuric spots and tendency to internal hemorrhages, albuminuria and hematuria, and severe general toxicosis.

The symptoms vary according to the geographic area of infection, season of the year and the virulence of the epidemic. It usually ends in apparent recovery, with perhaps some temporary(?) residual damage in the renal function.

2. Synonyms and nomenclature.

In the Japanese literature the disease was called by many names until 1942. It was often named for the locality where it was observed. One of its earliest names is 'fever disease' (39). The infection which occurred in 1938 July at Erh-tao-kiang was called the 'Erh-tao-kiang disease' or the 'Nidókó disease' (1).

In the fall of 1939 when the epidemic occurred at Sun-Wu or Sung-hua-chiang (Songó in Japanese) the First Research Team of the Japanese Army group under Maj. Gen. ISII reported it under the temporary name of 'Sun-wu fever' or 'Songó fever' (1; 9; 13). In the same year it was also known as infectious purpuric fever, endemic purpuric fever, acute purpura, and acute purpura-like nephritis (1). Another name from the same year is 'Hu-lin fever' or 'Kórin fever' (1; 9) named after the town Hulin in Tungan Province, north of Lake Hanka on the eastern Manchu-Siberian border.

In 1941 it was known as 'heiho fever' or 'Kokkó (or Kokukó) fever' (7). On February 19, 1942, the Japanese Army Order No. 989 provided an official name for the infectious disease. It was 'ryúkó-sei syukketu-netu' (1) (netu: fever). Its English equivalent is epidemic hemorrhagic fever (13). Nevertheless, the disease is occasionally called by other names, e.g., Manchurian epidemic hemorrhagic fever (HAYASI; 8).

The 1946 U.S. pamphlets added another name: Ta-yin-shan disease (13; 14) with the confusing remark that, according to some reporters, this term as well as the names 'Songó fever' and 'Kórin fever' were also used as synonyms of the so-called Kushan (or Koshan) disease, which seems, however, a different endemic disease of Manchuria as we will see later.

'Manchurian typhus', or the terms 'epidemic spotted fever' (14), acute spotted fever (14), eruptive typhus (14) should never be used for the designation of EHF. Similarly the name 'Manchurian fever' is a rather vague one though it was recently in the headlines (24 Nov. 1951) over a short announcement of the recent Korean epidemic (15). This term has already been used for the description of a Manchurian form of exanthematic typhus.

The Far-Eastern disease which the Japanese called Epidemic hemorrhagic fever' has been known to and described by the Russians (24 to 33) under the following denominations:

acute nephritis (1934 TARGANSKY), toxic capillaropathy, acute infectious nephritis (1940 ROTENBURG; 25), acute infectious nephroso-nephritis, infectious nephropathy, infectious nephroso-nephritis (so-called; after 1938), hemorrhagic nephroso-nephritis (1941 DUNAEVSKY; 27), Churilov disease (1935), nephroso-nephritis (1935), epidemic nephroso-nephritis (1941 TERSKIH; 31). But it was generally

felt that the term hemorrhagic nephroso-nephritis was a misnomer (27).

More popular terms for the disease were the following: 'six-day fever' (31), toxic gastritis, or 'so-called Manchurian gastritis' (33).

It was also suggested by Russian pathologists to call the disease 'acute endemic hemorrhagic diathesis', but such a term does not express the peculiarities of the Far-Eastern type of EHF. Perhaps a term such as 'apoplexy of the renal medullary substance' would be the closest to the actual pathological events in the kidney of EHF (28).

In spite of the different Russian and Japanese denominations there cannot be any doubt left, after one reads through the two sets of descriptions, that

the epidemic hemorrhagic fever of the Japanese and the acute infectious epidemic nephroso-nephritis of the Russian literature are synonyms for the same disease

which attacked the Japanese colonists and troops in Manchuria, the Russian troops and the inhabitants of slave-labor camps along the Lower Amur River in the Primorskaya, and the U.S. forces in Korea.

CHAPTER II

HISTORY AND GEOGRAPHY

1. History of epidemic hemorrhagic fever.

Epidemic hemorrhagic fever is probably an old disease in Manchuria (14), yet no similar infectious disease was reported, e.g., in the Russo-Japanese War of 1904-05 (23) though many cases of purpura were mentioned. It remains the task of historical research to detect the presence of EHF in previously recorded epidemics, especially in North Manchuria and East Manchuria (1).

In Chientao Province, people have known of a febrile disease which was prevalent among those dealing with hay (1). It is believed that the diagnosis of 'wool (facial) syphilis' of the older Chinese doctors in their death certificates also covered cases of EHF.

IBUKI states that several outbreaks of the epidemic have occurred in the Japanese Army in North and East Manchuria since 1935 but they were described under other diagnoses (39). In 1936 the so-called 'fever disease' broke out in an artillery unit at Botanko

after maneuvers in the swamps along the Sairin River (39). The 'scarlet fever' at Tang-ho (Doki) occurred in the troops in May 1937 (39).

Another epidemic with the features of EHF occurred in the Japanese Army in May 1938 (1). Another strange infection broke out in a cavalry regiment in July 1938 at Erh-tao-chiang (Japanese Nidókó) (1). The latter was described by Tukio IBUKI (6) and it was considered an atypical type of scarlet fever. Next year, however, it was identified with the Sun-wu epidemic (6).

In the months September to December of 1939 the epidemic was prevalent at Sun-wu (or Sung-hua-chiang; Japanese: Songó). It was first observed in a company of the Kwantung Army which was then advancing (39). It was then considered a new disease endemic in Manchuria (1). Maj. Gen. ISII and his seven assistants called it Songó fever.

In 1941 the same epidemic reappeared at Songó and Heiho, and in 1942 among the troops stationed at Korin (39). On 23 July 1943, the disease became epidemic among Japanese settlers in Pinkiang Province. The first case was considered sunstroke, and the patient was sent to the Harbin Central Hospital under such diagnosis. There he died, and the cadaver was autopsied 2 Aug 1943. Postmortem examination proved that Mr Sarukion died from EHF (1).

In the Russian Far-East the first observation of the epidemic was made in 1932. Epidemics occurred in 1933/34. A large number of cases were seen in 1935, from April on. Another epidemic broke out in the fall of 1935, but it was reported as a kind of 'leptospiro fever'. It regularly occurred year after year, with a maximum of 97 cases in 1939 (33). There were also smaller outbreaks at various locations, with 8 to 10 people sick at a time.

In 1939 and 1940 the Far-Eastern epidemics assumed larger proportions, and the research expeditions which were sent to the Russian Far-East had ample opportunity to study several hundred cases.

2. History of research on EHF.

Before the description of epidemic hemorrhagic fever Dr. Jettmar (pronounced: yet-mahr), a Viennese physician and serologist, who has been in Manchuria since about 1922, working at the Manchurian Plague Prevention Service with Lien-Teh Wu, discovered a mite on the dark-spined field-mouse (*Apodemus agrarius*) in Harbin in 1929. The mite was sent to Berlin for identification where in 1930 Count Herman VITZTHUM (pronounced: fits-toom) described it as *Laelaps jettmari* n.sp. (pronounced: leh-lops yet-mahr-ee). At that

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time the mite was suspected of playing some role in the transmission of plague only.

The Russian and the Japanese have equal merits in the recognition and study of EHF. Of course, the Japanese state that their military surgeons were the first who recognized the new disease unit (1) but such a claim is evidently erroneous.

a) Japanese research.

In July 1938, at the time of the Nidókó fever, the need for further investigation of the disease was felt. Research teams were organized by the Japanese Army. The first of such teams was sent in May 1939 for the study of the Sun-wu epidemic. It was in charge of Maj. Gen. ISII, and among the assistants was also Dr. KITANO.

In the same year, in December, Dr. ISIKAWA, the Director of the Pathological Institute of the Kanazawa Medical Faculty, reported his observations on the Sun-wa epidemic (6). Next year, at the March 1940 meeting of the Army Medical Association, the ISII group (27) suggested the virus origin of the epidemic.

Systematic study of the epidemic started about the time of the November 1942 outbreak at Sun-wu (1). In the fall of the same year SUZUE, professor at the Kuramoto Medical College and parttime professor at the Medical School of the Harbin Group of the Japanese Army in Manchuria, travelled through the afflicted region to collect pathological material for histological studies (2). Separate studies were made by KITANO, KIKUTI, KASAHARA, SAYAMA, KANAZAWA, NEZU, YOSHIMURA and KUDO.

In April 1943, KITANO reported on his parasitological studies to the Japanese Parasitological Society. He discussed the morphology and the habits of the vector mite which he named 'North-Manchurian mite' (1). In the same month he also reported on his virological studies (1). The geographical distribution of the mite and other parasitological studies were carried out especially by the ASAHINA Research Group (1).

The collected material on the epidemic disease was discussed in detail at various meetings of the many Japanese medical societies, including the Society for the Study of Infectious Diseases, the Parasitological Association, the Hematological Association, etc. In 1943 HONZIN has already stated that his article on the pathology of the disease was based upon 26 other Japanese articles (6), many of them having been published in the Journal of the Kanazawa Medical Association. (N.B. This journal was not available to me at the time of writing this review).

In 1944 Masazi KITANO, Maj. Gen. of the Japanese Army Medical Corps, wrote a comprehensive description of the epidemic which he

dedicated to the memory of the many Japanese officers and troops who became victims of the disease (1). At that time it was expected that the KASAHARA Research Team would soon report on the pathogenesis of EHF. Previously there was not much known on this subject though the Social Service Bureau of the Kwantung Army mentioned that it had prepared a few reports on the disease (1).

In 1944 a study was started on the month-by-month infestation of rodents with *Laclaps jettmari* in the Sun-wu and Chientao regions. When KITANO made his report the *Laclaps* study was not yet finished (1). In July 1944 HAYASI, who made himself known by his studies on the tutugamusi disease and the description of *Rickettsia orientalis*, spent some time at the Tungan Hospital in Eastern Manchuria in order to observe the pathogenic agent of EHF which he supposed to be a rickettsial organism. (And he remained in this belief even at such a late date as 1948.

Early in 1946 there were three U. S. government documents published which gave a brief summary of the medical aspect of the epidemic, referring to it by the name of EHF (13; 14; 19) but they did not know of any literature on the subject, neither Japanese nor Russian.

Immunological studies probably went on since the beginning of Army research into the causes of EHF. IKEDA says that his experiments with allergy in EHF began early, and that he had already in 1942-43-made his tests with the antigen described by him (See later; 41).

b) Russian research.

It may seem rather peculiar that the disease of epidemic hemorrhagic fever has been recognized and studied independently in Japan and in the Soviet Union, but described under different names (CAUTION: the disease which the Russian literature calls 'epidemic hemorrhagic fever' is not identical with the Far-Eastern type of EHF as it will be seen later), but neither the Russians nor the Japanese Army doctors have been aware of the studies carried out and the literature produced in the other's country.

Indeed, I was unable to find any Russian paper on infectious nephroso-nephritis which would quote any Japanese article on epidemic hemorrhagic fever; and vice versa! Hence, it may be a fair conclusion that my review is the first which identifies the disease under the different names and which brings together the findings of both groups.

Russian observations of the disease began to accumulate in 1932. MILLER, ILRIN, and CHURILOV described a few cases in 1935 when it was tentatively called 'Churilov's disease' and 'nephroso-

nephritis. In the same year CIGANKOV observed several cases of a peculiar disease which was called by common diagnostic terms and was defined only in 1938 (33).

But prior to that, there were three cases of acute nephritis described by TARGANSKY in 1934 (K klinike ostrogo nefrita), which were undoubtedly EHF, though the author did not report them as cases of an individual pathological entity, neither did he note their endemicity (25). It was also mentioned that perhaps the 'war nephritis' of 1914-18 had some connection with infectious nephroso-nephritis (HALPERIN; 32).

In 1936 CHURILOV studied the clinical course of the newly recognized disease. He stated that EHF is entirely limited to the Far-East (29).

In 1937 the disease was recognized by LEIBIN as an independent pathological and nosological unit (28). In the same year STEPANOV, TERSKIY and ROGOZIN observed a febrile disease which seemed to be an 'anicteric leptospirosis' due to virus (31).

Its regular occurrence in Far-Eastern Siberia pushed the disease into the center of interest among public health officials and physicians of the Red Army.

In 1938-39 NARKOMZDRAVA (USSR Public Health Agency) sent a research expedition to the Russian Far-East in charge of I. I. ROGOZIN for the study of the epidemiology and etiology of EHF. ROTENBURG and REZNIKOV, who were members of this research team, described their findings early in 1940. Another medical expedition in 1937 was under S. I. TARASOV (32).

Another research expedition was sent to the Primorskaya in 1940 under the leadership of the virologist professor A. A. SMORODINCEV. It was an expedition of VIEI (All-Russian Institute of Experimental Medicine in Moskva) for the study of the mysterious agent of the disease (29). Members of the VIEI expedition published a series of papers in 1940-41 (CHURILOV, LEIBIN, DUNAIEVSKY).

In addition to the expeditions from European Russia, a number of local Army surgeons stationed at the military posts in the Maritime District, in Spask, Voroshilov, Khabarovsk, etc. reported on the results of their independent studies of EHF (26).

About 1940, there was still much doubt as to the infectious origin of EHF (or, as the Russians called it, endemic nephroso-nephritis), and a number of physicians considered it a special form of scurvy (31).

Russian opinion about EHF is now, in 1951, so firmly settled that the disease is included in the latest pathological textbooks as a virus infection, but still under the old term of h e m o r - r h a g i c n e p h r o s o - n e p h r i t i s, and without any reference to Japanese research (e.g., A. I. ABRIKOSOV's Osnovy častnoi patologičeskoj anatomii, Moskva, 1950, p.420), while the term of e p i d e m i c h e m o r r h a g i c f e v e r is reserved in the Russian literature for other types of virus infection.

c) Other research.

In the U.S. the disease was briefly mentioned in 1946 in the government documents referred to above (13; 14; 19), but not until June 1950 was the disease identified by our military surgeons when they had an opportunity to observe it among the U.S. troops in Korea (15). Army research moves now towards the development of a specific preventive vaccine (15). It is hoped that this collective review of the literature will make a shortcut in our studies for the conquest of the disease.

From the papers one may assume that the U.S. Army initiated a very intensive research in Korea, Japan, and in the U.S. for the better understanding of EHF, for the isolation of the pathogenic virus and for the determination of the exact mode of transmission of infection (21).

3. Geographical distribution of EHF.

In general it may be assumed a p r i o r i that the distribution of the epidemic hemorrhagic fever of the Far-East coincides with the distribution of the reservoirs and vectors of its virus. This is more or less so though the original Japanese reports denied it. EHF has been observed high up in Northern Manchuria, above the 50th parallel, in Heiho, and on the other side of the Amur River in Blagoveshchensk. Recent observations show that it also occurs around the 38th parallel in Korea.

It may be also assumed at the present time that all the possible reservoirs and vectors of the virus are not yet known. Hence, the epidemiological area may be much wider than one would believe from the early descriptions of endemic outbreaks.

It was stated that EHF was limited to that part of Manchuria which is east of the Greater Hsing-an Mountain, and north of Chang-pai-shan (14), but the literature shows that it is also endemic in the Russian Far-East, that is, on the other side of the Lower Amur River.

Some of the towns and provinces of Manchuria where EHF was observed are the following:

At Botanko, along the Sairin River (1936), at Tang-ho (Doki; 1937) (39), Erh-tao-kiang (or Nidókó), a town in Mutankiang Province (1938) (1), at Sun-wu or Songó, a town in Heilungkiang-Province (1939), at Hulin (or Tungan) (1939), Heiho (1941), etc.

Most cases occurred in the marshy river-land of Northeastern Manchuria, especially in eight provinces: Sankiang, Tungan, Mutankiang, Chientao, Heiho, Pehan, Pinkiang, and Lunkiang (1; 36). In 1943 an outbreak was observed at Fularki (Fu-la-erh-hi) (1), also at the town of Tungnin in Mutankiang (36).

In November 1942, two cases were observed in Tungpei Hsien (in Pehan Province) by a doctor of the Ninth Chiutaokou Colonization Team (7). About 3 miles away from that place there was a village settled entirely by Koreans among whom the MIZUTA Team had observed two cases (7). The focus of epidemic was on the east side of the Peihei railroad line (7).

An autopsy case of KISIMOTO came from an epidemic in Chiamussu (11), a town at the Sungari River, near the marshy lowland of Northeastern Manchuria. In 1944 an outbreak of EHF was recorded from Chientao (: Kantó) Province, just above North Korea, near the Tumen River, and it was associated with exposure to hay (1).

According to Japanese observations, the ecological study of the virus vector *Laelaps* showed that the geographical limits of the mite are not identical with the geographical occurrence of the disease. It was especially noted that EHF was not seen in Manchouli at the northwestern border of Manchuria towards Mongolia, neither was there an epidemic in the South-Manchurian town of Chengchiatun (1). It is true that several cases were described from South Manchuria but these cases of EHF were supposed to have been contracted in North Manchuria towns, and only transferred to the south in their incubational stage (1).

The Russian reports are very hesitant to identify either the province or the town where their EHF occurred. It is evident, however, that the disease has a wide distribution in Russian territory, including such cities as Voroshilov, Spask-Dal'niy, Khabarovsk, Blagoveshchensk, etc. Many of the reports which I found in the literature came from these cities where the Russian research teams studied the disease, partly in the military hospitals.

(C. F. Mayer: Epidemic hemorrhagic fever)

In 1944 the Japanese military surgeons were certain that the disease was also prevalent in the neighboring districts of the Soviet Union (1). They said that the distribution of EHF roughly coincides with that of the Russian tick-borne encephalitis (the Far-Eastern or spring-summer variety) as far as Manchuria was concerned. In 1944 the Japanese were in possession of an epidemiological map which pointed out the Russian towns of the Far-East where EHF had been observed. It should also be remembered that the Russian side of the Lower Amur River is a marshy low-land where, according to several recently published maps, there are many slave-labor camps, factors which are favorable for the breeding of all kinds of epidemics.

U.S. newspapers and other announcements show that during the current Korean incident the disease has been observed among U.N. troops fighting in Korea (15). Previous Japanese experience also shows that it is possible to contract the disease in Manchuria and to become sick with it in places remote from the site of endemic disease. Thus, captured prisoners may suffer from an infection of this type.

The transfer of the infection is proved by a Japanese newspaper report in 1943 which stated that a soldier who returned to Hokkaido, the northern island of Japan, from the Manchurian Army came down with EHF in Japan (7).

Whether the Far-Eastern type of EHF occurred also in other parts of the world where it was perhaps described under the names of other infectious diseases, or mis-diagnosed as another type of infectious hemorrhagic diathesis remains an open question which can be answered after the re-examination of a large bulk of the medical literature and of a large file of the original postmortem or clinical records only.

Further development on the ecology of the disease could be expected from the study of the life-habits of the vectors of EHF. Notably, it is not clear whether the disease can be contracted at all altitudes where the *Apodemus agrarius* and other vertebrate hosts of the vectors may be found.

Most of the reports so far stress the fact that EHF was observed along the rivers, in lowlands, swampy regions, etc.

The chief host of the *Iaelaps* mite, i.e., *Apodemus agrarius* is a very common field-mouse, all over the world, and can be found as far south as the island of Formosa. (See the next chapter)

(See the attached map of Manchuria)

MAP OF MANCHOUKUO

SCALE: 1:6300,000



LOCATOR TO MAP

Reduction of map ca one-half from
its original scale of 1:6,300,000.

Blagoveshchensk C 2
 Botanko (not identified)
 Chang-paishan (not identified)
 Cheng-chiatun B 4
 Chiamussu D 3
 Chientao (Kantó) Province D 4
 Chin-hsien B 4
 Doki (not identified)
 Erh-tao-kiang (not identified)
 Fularki B 3
 Harbin C 3
 Heiho (Kokkó) C 2
 Heilungkiang Province C 2 - D 2
 Hulin E 3
 Khabarovsk (Habarovsk) E 3
 Kokko : HEIHO
 Korin : HULIN
 Koshan or Kushan or Kashan C 3
 Kwantung District B 5
 Lungkiang Province B 3
 Manchouli A 2
 Mutankiang Province & Town D 3
 Nidókó : ERH-TAO-KIANG
 Pehan or Peihan Province C 3
 Peihei Railroad (from Peian to Harbin)
 Pinkiang Province C 3
 Pinkiang Town : HARBIN
 Primorskaya F 3
 Sankiang Province D E 3
 Songó : SUNWU
 Sunwu or Sung-wu or Sung-hua chiang C 2
 Spask-Dal'niy E 3
 Tang-ho : DOKI
 Tungan Province E 3
 Tungan Town (Mishan) D 3
 Tungning or Tungnin D 4
 Tungpei hsien C 3
 * * * * *
 Amur River B 1, C 1 2, D 2 3, E 2 3 F 2
 Lake Hanka E 3
 Sairin River (not identified)
 Sungari River C 4 3, D 3, E 3
 Tumen River D 4 (at Korean-Manchurian Border)

CHAPTER III

EPIDEMIOLOGY

1. Predisposing factors.

a) Age incidence.

URONO described a case in a 58 yr old Manchurian coolie whose job was the gathering of dry grass and hay for the Japanese Army (7). His other patient was a 19 yr old youngster. In general, most of the patients were young adults between the ages of 20 and 30. The afflicted persons in Spask were of the same age range during the 1938-39 epidemic (26; 28).

LEIBIN had not seen a single case in children, adolescents, and in persons over 30 years of age (28). Others reported, however, several cases in people over 45 years. Among CIGANKOV's patients 96 were between 20 and 24 years of age, and 27 were older (33). He also observed a family in which six members became sick, one after another, including three small children aged 2, 6, and 11 years (33).

b) Nutritional status.

Most of the afflicted people were in good general health (30), strong (28), normally developed and in a good nutritional status. In CIGANKOV's series, 102 patients had normal body build, 20 were athletic, and 3 asthenic (33).

c) Sex incidence.

According to Russian observations the EHF was less frequently seen in gynecological and similar other therapeutical establishments (26), though the female sex is not considered more resistant to the disease than the male (30). By their usual occupations, women and girls are perhaps less exposed to the disease.

d) Racial incidence.

Early observers stated that EHF was rarely observed among native Manchurians (1944; 1) while pioneer Japanese colonists were easy victims of the disease. BELONOSCHKIN pointed out that the Japanese colonists, the immigrant farmers, were not prepared for the rough, cold climate in Manchuria (71), and their clothes were not sufficient protection in pioneer work.

On the other hand, some of the Japanese colonization teams came across villages which were entirely inhabited by Korean immigrants and where the disease was prevalent (7). Russian doctors

noted that EHF was rarely seen in inhabitants of urban areas (25).

2. Climatic and seasonal incidence.

Though sporadic cases of EHF can be seen the year around, the epidemic outbreaks occur everywhere so that there is a regularity between the region, the weather, the external temperature and the season in which the incidence of the disease is at its highest peak.

The Japanese in 1944 reported two epidemic peaks: One in May-June in the spring, the other in October-November in the fall (1). Others (13) stated that the highest peak occurs in the period from late summer to the end of December. This has also been the experience of the U. S. Army in Korea (15).

Above the 50th parallel, in Heiho, the epidemics of EHF come early in April and in November. The same cycles prevail in the region of the Lower Amur River. At places situated southward it also occurs in April and May (14).

In East Manchuria the greatest seasonal incidence of EHF is from May to September, and in North Manchuria from September to November (42) according to Japanese Army observations. Another source puts November as the most favorable time for the development of small epidemics of EHF (7).

In The U.S.S.R. it occurred mostly from May to October--November, with a maximum in late summer or fall (25; 30; 31). At Spask, 22 cases were treated in 1938-39, which-occurred in the following months: Jan. 1, May 2, Aug. 1, Sept. 2, Oct. 12, Nov 4 (26).

The 125 cases reported by CIGANKOV from the Primorskaya had the following distribution according to months and years (33):

	1935	1936	1937	1938	1939	Total
July					14	14
August			1	1	16	18
September	1	1	3	3	45	53
October		1	4	10	20	35
November	1		1	1	2	5
Total	2	2	9	15	97	125

Experiments on the virulence of the virus proved that cold weather has no damaging effect upon the pathogenic agent; that, on the contrary, the extremely cold districts of North Manchuria may create the optimal condition for the survival of the virus and the existence of the disease (1).

3. Method and source of infection.

In spite of very close contact of people in a family, or in a Russian collective (33), under crowded conditions, with insufficient isolation of patients in the therapeutic institutions, etc. not a single case of proved contact transfer of EHF was seen (26). There is no person-to-person infection (1944; 1), in short, no so-called human carriers of the infection (25; 30; 33). Nurses in the hospitals were not infected (30), and there was no observed 'ward infection' (30).

The Russian CIGANKOV is the only one who described a small outbreak of the disease in a family (33). On the other hand, it was often mentioned that the disease was rather frequent among army troops who lived in barracks, tents, camps (1) and training camps (1).

There were certain places which seemed to be more contaminated than others. Within such an area civilians in military service, families of Japanese soldiers, and pioneer settlers were affected indiscriminately (1). Sometimes an entire regiment was attacked.

In 1944 it was observed in the Japanese Army that in some divisions most of the infected patients belonged to a special company, or they lived in a certain tent or house. Inhabitants of the first story of a dormitory seemed to be more exposed than those living on the second floor (1). Again those who had their bunks near the exits and entrances of tents showed a higher incidence of infection (1). For the clinical description of EHF Maj. Gen. KITANO used his observations gained from the outbreak of the disease in the 'Nagayama Company' (1).

It was noticed that many of the infected people had close relation with straw (13) and hay (transportation and storage) used both as fodder for horses and bedding in the tents (1; 34; 39). Outbreaks occurred also among troops engaged in fortification work (13). In the Manchurian provinces where the disease has been known for a long time, people said that the fever attacked those who handled hay and grass (1). Those who gathered grass and hay from swampy strips of land seemed to be especially exposed to the infection (7).

The sites of the outbreaks of EHF are plagued by various rodents, rats and mice (33). Tent-dwellers often said that the rodents came and went unobstructed (33). It was found that some of these rodents were infested with the mite *Ia claps*, the carrier of the virus of EHF. It was then thought that when the rodent moves about, its mite may stick to grass, hay, or the ground near the rodent's nest, and from there it may get on people's clothing (1).

It is also possible that the mite sticks to the grass and hay when rodents invade the storage place of litter and fodder (1). There was no evidence of transmission of the infection by means of drinking water, or food (26), or the contact with contaminated water in rivers (31).

TERSKIH observed that the cases of infection which occur in an outbreak are not concentrated at a single place (31) but may be spread to many settlements. In an epidemic in 1939 cases of EHF were seen at 58 different settlements within the area of epidemic.

4. The attack rate and spread of the outbreak.

The Japanese reports do not tell much of the epidemics prior to 1941 (1). Some of the reports of the Social Service Bureau of the Japanese Kwantung Army mention a few statistical figures. In 1941 there were 32 cases observed with 5 deaths; in 1942, 77 cases. Among them were 19 cases from Chinh sien with 4 deaths, but a later inquiry showed that the deaths were due to relapsing fever and not to EHF (1).

From another source it is known that in the September-December period of 1939, 20 Japanese soldiers contracted the disease at Sung-wu, and 6 of them died (39). In 1941, at Sun-wu and Heiho, there were 236 infected persons 26 of whom died (39). The Korin epidemic affected 102 patients in 1942 (39).

Scattered outbreaks with up to 50 or more cases have occurred (13). In the 1941 epidemic at Heiho 10 o/o of the troops became sick. In October 1942, at an Army post near Hulin, 40-50 men contracted the disease in a regiment of ca 5,000 (13). Epidemics in 1944 were of small extent. This shows that as an epidemic the disease is perhaps not serious though it may be a serious ailment for the afflicted individual. In 1941, at the Sun-wu Army Hospital the relative incidence of EHF was estimated 30 o/o, when its true incidence might have been but 1 o/o (14).

In Tungnin township (Mutankiang) there was a small epidemic in a Japanese Army Corps. It included 17 definite cases, and 7 suspected cases. There were 2 fatalities, 2 severely sick patients, the others showed a light course of the disease (NOMURA; 36).

The Russian cases occurred sporadically the year around, or in comparatively small epidemics affecting 3 to 10 people at once. It was also noted that the outbreaks never left so-called 'tails' (25). People working at unhealthy places, or performing agricultural duties seemed to be more exposed to EHF, and the spread of the small epidemics showed that the possible reservoir of the virus is some rodent (26).

5. Environmental factors.

The disease is prevalent in the marshy, swampy regions along the rivers of Northeastern Manchuria and the Russian Far-East (1; 7), but its occurrence in hilly and forest areas has also been noted (TAKAMI; 39).

In an epidemic around Chiutaokou it was found in 1942 that the two Koreans who became sick were living in a settlement on a swampy strip of land and that a coolie and a Japanese youngster who contracted the disease in Chiutaokou used to move freely between the town and that settlement in gathering dry grass for the Army (7). Since rodents are involved in the transmission of the disease it is natural to find a higher rate of exposure to EHF at places where the food is stored or where the kitchen equipment is kept (1).

In CIGANKOV's series, 40.2 o/o of the patients could not attribute their sickness to any cause; 28.2 o/o of them blamed it on hard work, unhealthy places, etc.; 21.7 o/o believed that it was due to exposure to cold; and 4.5 o/o thought that the disease was caused by some kind of vegetable food (33). Lack of cleanliness in general, and dampness of the dwelling places seemed to be a contributing factor to a higher incidence of infection (1).

In the Primorskaya the patients reported exposure to cold, bathing in very cold mountain rivers, sleeping in tents in the open in inclement weather, working in damp, insanitary places, etc. (26).

6. Animal reservoirs.

The carriers of the natural virus seem to be rodents (1). These are described in the next section ('Vertebrate hosts'). Other animals which appear to be naturally infected by the virus of epidemic hemorrhagic fever are the horse and the cat. This point, however, needs further study.

It was the Russian CIGANKOV in 1941 in whose paper I found the first reference to a higher incidence of EHF among people who were in contact with horses. Among his cases, 60 o/o to 70 o/o of the afflicted were such people. He then assumed that the virus of the disease might be present in the water of the river where the horses were regularly bathed (33). The Japanese had a similar experience with cavalry-men, hostlers, and people who provided hay fodder for horses (1; 44).

As to cats CIGANKOV reported the story told by a family about their three cats during an epidemic outbreak of EHF. The cats became

sick. They began to vomit, showed anxiety and restlessness. They refused food but kept on miaowing; finally they died. CIGANKOV (33) made bacteriological and serological examinations of the feline cadavers, but could not find anything unusual.

7. Vertebrate hosts.

It was noted by all investigators that the places of infection with EHF abounded with all kinds of rodents, field-mice, water-rats, house-mice, etc. (1). In November 1942 many rodents were caught and their parasites used for experimental study of the probable virus of EHF (1).

When it was recognized that *Iaelaps* was a vector of the virus, various rodents were examined to determine whether they harbored the mite. Among the Japanese workers the ASAHINA Research Group studied the parasitic hosts of *Iaelaps jettmari*. They found that the largest number of the *Iaelaps* mite infested the dark-spined field-mouse, called 'sesuzi-nezumi' in the Japanese and identified with *Apodemus agrarius mantchuricus* (1).

It was noted that in Sun-wu and Chientao the number of *Iaelaps* parasites increased on *Apodemus* during the epidemic outbreaks in 1944, and a month-by-month count of the parasitic mite was suggested (1).

Japanese studies also showed that there may be other vertebrate hosts on which *Iaelaps* mites are parasitic. These other rodents are also in great abundance in marshy regions and along the river banks of Manchuria. The habits of all these rodents should be known for a successful control of the disease (1).

KITANO's parasitological studies revealed that other mites, perhaps closely related to *Iaelaps*, may be vectors of the virus. He found such mites (his No. 1 and No. 3) on the field-mouse which he called 'yosihata-nezumi' (nezumi : rat or mouse) and on the ordinary water-rat (*Rattus norvegicus*) which harbored the mites called by him No 2 and No. 3 (1).

According to recent U.S.Army experience, squirrels may also be hosts to such mites as are able to become carriers of the virus of EHF (15). Various other rodents are also under suspicion.

a) *Apodemus agrarius mantchuricus* Thomas 1898.

Apodemus agrarius, commonly called a field-mouse, is very common to the fields of Europe and Asia. It occurs from Iceland eastward to the Pacific, across the Soviet Union, from Scandinavia southward to the Mediterranean Coast, also in Asia Minor, Turkestan, Manchuria, Korea, China, Sakhalin, Mongolia, many other Asiatic countries, Formosa, the Riukiu Islands, also Morocco, Algeria, etc. (73).

It is very resistant to cold, and it may live in the mountains 4000 to 5000 feet (1,600 m) above sea level (75). SVIRIDENKO says that the field-mouse cannot stand dry weather; it must seek moist and swampy regions where mass propagation is possible but it does not like the real swamps and marshes (1). It can be found in forests, in gardens, shrubs, around dwellings. It-eats seeds, berries, roots, green parts of plants, and insects.

The field-mouse is a poor digger. Its burrows are not very deep (75). Its nesting habits are the following:

The nest is 10-30 cm below the surface of the ground. It may have one entrance, or several, mostly two, each being from 2.5 cm to 3 cm in diameter. The length of the tunnel is from 50 cm to 150 cm. The nest is usually built so that the middle of the tunnel is taken by an oval, 10 cm to 15 cm wide. The nests are chiefly found on the slopes of river banks flowing through the plains of North-eastern Manchuria. An-uneven ground, with much soil in the grass-land, is preferred (1). It-is found, however, in forests as well as in the open country (72).

The *Apodemus agrarius* in the Far-East can be found as high up as the 65° Lat. North, and as far south as Formosa. It has a number of subspecies in the various countries of the Far-East, such as

- *Apodemus agrarius coreae* (Korean field-mouse)
- *Apodemus agrarius mantchuricus* (Manchurian field-mouse)
- *Apodemus agrarius ningpoensis*
- *Apodemus agrarius pallidior* (72).

The Korean variety was described by Thomas in 1908 after a specimen found 110 miles SE of Seoul, in Minyong. According to HAYMAN (73) the characteristics of this group, i. e., the Far-Eastern type of *Apodemus agrarius*, are a supraorbital ridge, and a black mid-dorsal stripe from which the field-mouse has its Japanese name, 'sesuzi' meaning: 'seam along the backbone'.

The size of *Apodemus agrarius* varies from 95 mm to 118 mm, not including the tail. The tail is about 78 mm long, the hind foot is 19 mm, and the ear measures 14 mm.

As it was pointed out to me by Dr JOHNSON, of the U. S. National Museum, the ear of this type of field-mouse is considerably large and this feature makes it easy to differentiate *Apodemus* from *Microtus*.

As the attached illustration shows the most characteristic feature of the Far-Eastern type of *Apodemus agrarius* is the dark stripe along its spine. This is typical of all four subspecies. (The illustration shows the species common in Formosa).

Russian studies showed that the Manchurian field-mouse has a considerable mobility and is apt to come in contact with many. Hence, as suggested by SVIRIDENKO (75), it could become an important factor in the propagation of various virus diseases. The field-mouse itself has a low susceptibility to several diseases. It was shown by Russian investigators that the *Apodemus agrarius* is immune to encephalitis but it may become the carrier of this disease (75).

Apodemus agrarius harbors a number of arthropod parasites, such as *Iaelaps*, *Ixodes persulcatus*, and *Ixodes ricinus*, all of which are known to be vectors of virus infections.

8. Arthropod vectors of EHF.

Before the *Iaelaps* mite was recognized as the chief vector of EHF, several other arthropods were examined for their possible role in spreading the infection. The role of lice and other bloodsucking insects was studied by Maj. Gen. ISII and others. In 1940 the Russians had not yet detected an arthropod vector (25).

In an epidemic which was observed at Fularki it was seen that the captured rats harbored an unusual number of ticks (whether a true tick is meant or a true mite is not clear from the Japanese text) (1). Also many fleas were caught on men during the epidemic outbreaks of EHF in a Japanese Army regiment but the fleas could not be demonstrated as carriers of the virus (1).

At the discovery of EHF, when there was a suggestion that it might be caused by an unknown rickettsial organism, it was also thought that the carrier might be a tick of the *Dermacentor* genus (13) or one of the flea species parasitic on rodents.

It was stated that the common house tick (of *Ixodidae*) and the *Iaelaps* mite have similar feeding habits (1). Both may attach themselves to rats and suck blood. Hence, it was supposed a *p r i o r i* that a common tick, when infected, could become the vector of the virus (1).



(C.F. MAYN: Epidemic hemorrhagic fever)
(Washington, 1951 December)

Apodemus agrarius PALLAS ca. $\frac{1}{3}$ life size

a) Laelaptid mites as vectors of EHF.

In a recent (1950) article, Capt. H. L. KEEGAN outlined briefly that laelaptid mites are vectors of several diseases. He did not mention ENF, though.

The role of laelaptid mites in the carriage of the pathogenic organism of EHF was studied by KITANO who found several species on rodents (rats), and numbered them from No. 1 to No. 4, preparing an entomological differentiation and identification chart for their morphological characteristics as follows: (1)

M i t t e

I. Dorsal and ventral setae short and thick No. 1

II. " " " " long, fine, hairlike:

a) Ventral plate square; posterior end & genital plate concave No. 2

b) " " wider than long; genito-abdominal plate not concave:

1. Ventral plate divided by transverse line into two Laelaps jettmari

2. No division of ventral plate:

a) Anal plate horn-shaped No. 3

b) " " 4-cornered, posterior end semicircular No. 4

The family of Laelaptidae includes about 75 genera (VITZTHUM) many of them being parasitic on rodents. The genus Laelaps has ca 30 species which are found all over the world. Some of them are in tropical countries, others in areas exposed to the Asiatic winter (12). The presence of Laelaps mite has not been established in Korea, according to TAKAMI (39).

b) *Laelaps jettmari* Vitzthum 1930.

The chief regular vector of the virus of BHF is the so-called North-Manchurian mite (KITANO) (1), or *Iaelaps jettmari*. It is supposed that by the bite of this mite the virus is injected into the human bloodstream (1).

Dr. JETTAR found the mite in the fall of 1929 near Harbin on *Cricetulus griseus*, and also in a nest of *Apodemus agrarius*. Dr. JETTAR was associated at that time with the Harbin Plague Prevention Service where he carried out a very extensive research not only into the epidemiology of plague but also into the natural history and anthropology of Manchuria. He was graduated from the University of Vienna where he had been working for some time as a serologist. He probably came to Manchuria after World War I.

When in 1929 he found the unknown mite on *Cricetulus* he sent it to Count Hermann VITZTHUM (1879-), famous acarologist and associate at the Berlin Veterinary High School for identification and description. Dr VITZTHUM gave to the mite the new species name: *Laelaps jettmari*, while the term of 'North-Manchurian mite, or tick' (in Japanese) was given to the parasite by KITANO since he considered that the mite is found in the northern part of Manchuria and-is the vector of a disease which is endemic in the same area (1).

- Japanese reports also refer to the mite by the term 'togedani' (9). The ASAHINA Research Group found that *Laelaps* is widely distributed in Manchuria. It was found on rodents in Chengchiatun, in South Manchuria as well as in Manchouli, high up in Northwest Manchuria though epidemics of EHF were not observed at either place (1). Besides being a vector of the virus of EHF this species of *Laelaps* is also a vector of tutugamusi (or tsutsugamushi) disease, according to HAYASI (9).

According to the original description of VITZTHUM, *Laelaps jettmari* is very similar to the European mouse-mite, *Laelaps muris* (Ljungh, 1799). His-original description was based upon that of an adult female form. The length of idiosoma of the specimen described by VITZTHUM is 0.740 mm, its width 0.530 mm. It is rather flat, but there are some depressions over its supraesophageal ganglion where the dorsal shield is decidedly weaker in chitin than farther back, and these softer spots are most probably related to light perception.

The hairs on the trunk, their number and arrangement, are the same as on the well-known European species. The hairs on the back are not shorter or thinner than on the sides (more or less as those of *Laelaps hilaris*). -The posterior pair of setae is very short, almost imperceptible. On the ventral side the adanal hairs are also very short-and in sharp contrast with the single, very long post-anal hair.- The Peritremata reach over the Coxa I, as in most *Laelaps* species.

KITANO attempted to give a fuller description of the male and female forms of *Laelaps jettmari* (1). His description reads as follows:

The female *Laelaps jettmari* has a 0.75 mm x 0.53 mm ovoid or round body, with oval convex scutum, which has a narrow posterior extremity, and has 6-8 setae on the scutum of the same length and width as at the side of the body. The ventral side is hexagonal, wider than long, concave. The greatest width of the body is about one-third-from the posterior end. There are 3 pairs of setae on each side. The genitoventral plate has 4 pairs of setae. The anal plate resembles a seta, and the very small spiracles are located

along the anterior half of the body. The mouth-part is armed with very small denticles (1). The ventral plate is divided by a transverse line.

The male has a somewhat smaller and narrower body than the female (0.57mm x 0.45mm). Its shield is oval, longer than wide, narrowing towards its posterior extremity, with 6-8 rows of setae along the sides of the body, of equal length and width. The genital and anal plates on the ventral surface are fused together, forming a large ventral plate.

The greatest width of the male is at the level of the 4th pair from the posterior end. There are about 10 setae, disregarding the 3 anal setae. The perianal setae are shorter than the terminal ones. The mouth-part is blunt, and is provided with no denticles (1).

The female of the mite (*Laelaps jettmari*) carries the eggs in its body to full maturity. The young stage hatches from the egg while still in the genital tract of the female; then it is discharged as a young, 6-legged larva. The larva undergoes a change into 'first nymph' and 'second nymph' in the nest of the field-mouse, before it assumes its final adult form (1). Its entire development may not take more than 2-3 weeks from its outward emergence to its adult stage.

The tick likes to hide on the posterior aspect of the hind foot of *Apodemus*, but could not be observed among the hairs of the head of the mouse, contrary to the behavior of the ordinary tick. (1). In his report VITZTHUM mentions that *Laelaps jettmari* is blood-sucking.

Most of the Acarina, however, which were sent to him from Manchuria contained no blood in their intestines, not even the so-called 'Haemo'-gamasus *manchuricus*. But *Laelaps jettmari* is an exception. Hence, it is a possible vector of any infectious disease, even of plague (12).

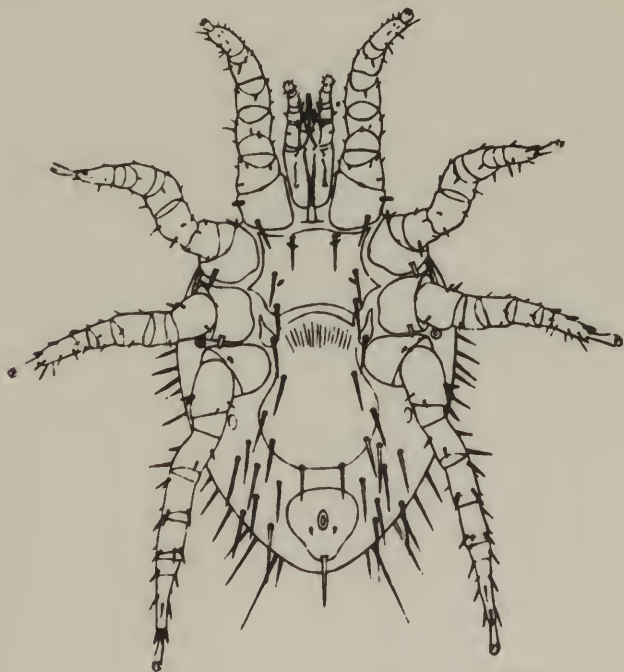
On the other hand, according to our present knowledge of the habits of the mite, it is unthinkable that *Laelaps jettmari* ever attacked a man. Even if it would feed on the plague-infected blood of a rodent, it would be impossible to expect the mite to transfer the plague to a man, according to VITZTHUM (12). (See Chapter VII: Pathogenesis : Portal of infection).

* * *

NOTE. According to JETTAR, the *Apodemus agrarius* which he caught near Harbin was found to be infected with trypanosoma in 4 o/o, grahamella in 5 o/o. He also found mixed infection of grahamellasis and bartonellasis in some of the field-mice (74).



The North-Manchurian mite (*Iaelaps jettmari*, n.sp., Vitzthum 1930); reprinted from Zool. Jahrb., Syst. Oekol., 1930, 60: 406-407. Dorsal view above, ventral view below. (C.F. MAYER: Epidemic hemorrhagic fever) (Wash., December 1951)



CHAPTER IV

CLINICAL COURSE

The first Japanese clinical descriptions of epidemic hemorrhagic fever were made by IBUKI and NAGAYAM after the 1938 epidemics. Two cases were described clinically by K. URUNO, 'Doctor of Technical Medicine for Greater Asia', in 1943. The cases were referred to him by an M. D. of the Sixth Heimaliu Colonization Team (7).

In the Japanese records there were very few observations on the clinical course of EHF while these records abounded in pathological and etiological details. The case of a private first-class of the Corps of Volunteers in the Japanese Army was described with acute observation by Maj. Gen. KITANO (1). This patient was hospitalized in the prodromal stage of the disease so that the full course of the infection could be carefully studied.

The Russian reports in general give a much more detailed description of the clinical course than could be found in the Japanese papers, at least according to my impression gained from reading the journal articles on EHF.

In both countries the first clinical descriptions contained many contradictory data, and there was even serious doubt as to the nosological individuality of EHF (28). The best clinical description on the Russian side was written by REZNIKOV, Army surgeon who in 1939-40 was stationed in the Military Hospital at Spask-Dal'niy. His report is based upon 22 cases (26).

The duration of the main symptoms of EHF was sufficiently well tabulated by a Navy pamphlet published in 1946 (14). They included flushing of face (1. to 10. day), congestion of the conjunctiva (2. to 11. day), reddening of pharynx (2. to 9. day), hemorrhages (3. to 8. day), nausea (1. to 9. day), insomnia (1. to 8. day), albuminuria (4. to 12. day) and fever (1. to 8. day).

1. Incubation period, prodromal stage, onset.

- The latent period of infection varies from 0 to 4 weeks (1; 34). The average duration of the incubation period is from 2 to 3 weeks (1; 42). In experimental infection of monkeys the incubation period was 19 days in one group, and 12 days in the second group which received the virus after an animal-passage (3). A definite prodromal stage occurs only in single cases according to the Russians (25), and it may be marked by slight headache and general indisposition. KITANO reported that a private sought medical aid when he felt profuse nocturnal sweating. Another Japanese source stated that in about 50 o/o of the cases there was a definite prodromal period of from 1 to 2 days duration (42).

Most reports spoke of a sudden onset of EHF, with a slight fever for 1 to 2 days, followed by chills, shivering, and sudden development of high fever as it developed in members of the Nagayama Company (1).

2. Clinical symptoms.

Among the early symptoms there may be various pains, rheumatic articular or myalgic in the limbs, general malaise, and indisposition (26), nausea with repeated vomiting, headache which is localized in the forehead and the occipital region (26). Even stammering was mentioned as an early symptom (13) in a U.S. pamphlet.

According to the newspaper reports, our Korean cases began with diarrhea and headache, which was followed by fever, chills, joint pains, nausea and vomiting.

A case with mild course, observed in a youth of 19 years, showed the following development: (7)

1st day:- pain in the loins and limbs, and slight congestion of the bulbar conjunctiva.

2nd day:- chill and fever up to 39.5°C , headache, lumbar pain and pain in the limbs; vomiting and albuminuria.

3rd day:- the fever subsided, the pain lessened, the conjunctival congestion disappeared, and the nausea ceased; there was a small amount of nosebleed. The patient was considered completely 'cured'.

In the milder cases, or in those recently seen in Korea (1951) the symptoms usually subsided by the 7th day of sickness (15). A fatal case of about 2-weeks duration was observed in an older man. Its chief symptoms followed in this sequence: (7)

1st day:- lack of appetite, headache, lumbar pain, arthralgia and myalgia in the limbs, chills and fever up to 40°C , lasting 3 days.

2nd day:- flushed face, congestion of bulbar conjunctiva, puffiness of face, and large amount of protein in urine.

3rd day:- increased congestion of conjunctiva, severe nausea, appearance of hemorrhagic diathesis, with subcutaneous ecchymoses on the upper arm; Rumpel-Leede test (tourniquet) positive.

4th day:- increase in number and in size of multiple hemorrhagic spots on skin, hematuria. The fever subsided.

5th day:- lessening of hematuria; severe nausea as before, hiccup, hemorrhages on the mucous membranes, epistaxis, bleeding gums. Bleeding and vomiting lessened somewhat but the hiccup continued until the 9th day.

10th day:- great weakness, sunken eyeballs, cerebral symptoms with delirium.

(C.F. MAYER: Epidemic hemorrhagic fever)

11th day: - dyspnea which progressed in difficulty.
13th day: - death.

a) Stages of clinical course.

CIGANKOV distinguished 3 stages of the disease: 1. febrile period, 2. afebrile period, and 3. convalescent stage (33). This is, of course, an artificial division but it was accepted by a number of authors (25; 29). Each stage of the disease is marked by special clinical characteristics, corresponding to special pathological changes in various organs and tissues.

The first stage or the febrile period may last from 3 to 8 days. The second stage or afebrile period is connected with the development of renal lesions; it may begin exactly at the return of the temperature to normal, or it may start a few days earlier or later. It is of quite short duration. The symptoms of this stage reach their maximum in a few days, and then they subside in a few days.

The third stage is the period of convalescence, which in the majority of patients will end in full organic recovery.

b) Clinical varieties.

The clinical course of EHF runs in a mild and in a severe form as seen above (26).

A much more definite classification was made by CIGANKOV in 1941 (33). He was able to distinguish 4 clinical varieties of EHF according to the predominance and combination of clinical signs and symptoms. These four varieties are the following:

1. The grippal-typhoid form. It shows signs of general toxicosis and infection, with slightly pronounced renal lesions. It occurred in 26.6 o/o of the cases. There was flushing of the face, congestion of conjunctiva, catarrh of the respiratory tract, abdominal colic, nausea, constipation, headache, loss of appetite, and oliguria with thirst. Sometimes there were symptoms indicating a few slight changes in the neuropsychic sphere. The fever usually ended in 5-7-9 days. The form included the comparatively mild cases.

2. The gastrointestinal form. It resembles some of the following diseases from which it has to be differentiated: acute gastritis, infectious enterocolitis, paratyphoid (or food poisoning), sometimes typical 'acute abdomen'. It occurred in 45.5 o/o of the cases. Many of the cases which occurred during the 1938-39 Russian Far-East epidemic assumed this form. There

is usually much damage in the kidney, and this form is of moderate severity.

3. The u r e m i c form. It occurred in 24.4 o/o of the cases. It is dominated by manifestations of the renal damage, and development of azotemia or eclamptic uremia. This form is of serious prognosis.

4. The m e n i n g o - e n c e p h a l i t i c form. This is the form which usually ends in coma and death. It occurred in 5-6 o/o of the cases. There are marked renal symptoms, and secondary toxi-infectious encephalitis, pathological reflexes, serious headaches. The symptoms of the affection of the central nervous system usually appear after the acute symptoms of the renal lesions have subsided.

3. Symptomatology of EHF in detail.

a)) The face.

The face is flushed. It looks as if it were suntanned (36) or as if the person were under the effect of an alcoholic intoxication. There is a certain amount of facial puffiness (1), thereby resembling the faces of patients suffering from exanthematic typhus (25). Russians compared the color of the hyperemic face to cyanosis and to the color of red copper (25). The nasolabial triangle remains white (CHURILOV 29).

Now and then there may be a slight puffiness of the e y e - l i d s, but there is no definite edema (25). Puffiness occurred only in 2 out of 22 cases of a Russian series (26).

In the second stage there may also be petechial bleeding on the face, especially on the f o r e h e a d (32).

The conjunctiva is congested, but there is no pericorneal hyperemia (1). The e x p r e s s i o n of the patient is remarkably stupid (1). In the neck one may find the thyroid slightly enlarged (22.4 o/o) (26).

b) Pain.

The onset of the disease is characterized by frequently violent, rheumatic, or myalgic pain in the limbs, especially in the lower limbs, and by lumbago (25).

The postfebrile second stage may be marked by abdominal pains which resemble those of appendicitis, or by colic resembling that caused by an ureteral stone (1). The pain in the lumbar region is

caused by the lesions in the kidney (25). Lumbar pain appears with sudden violence, with some severity, but after a few days it may suddenly subside, thereby marking the beginning of the period of convalescence and recovery (25).

c) The fever

The entire febrile period may last from 3 to 8 days, almost always 5-6 days (25). Hence, on the Russian side of the Amur EHF is also called "6-day fever" (31).

The sudden onset is usually with a slight fever of 1-2 days; then higher temperatures develop, with chill and shivering (1). The fever reaches its maximum in 2 to 5 days (25), then it drops by crisis or lysis (26) to subnormal level.

In Korea, temperatures up to 104° F. have been observed (15), which kept on for 3-4 days. According to the Japanese observations, the duration of high fever is from 3 to 5 days, in serious cases a week (1) or even 8-9 days (25; 26; 42); then it returns to normal in 2-4 days.

There are several possible types of protracted fever, however:

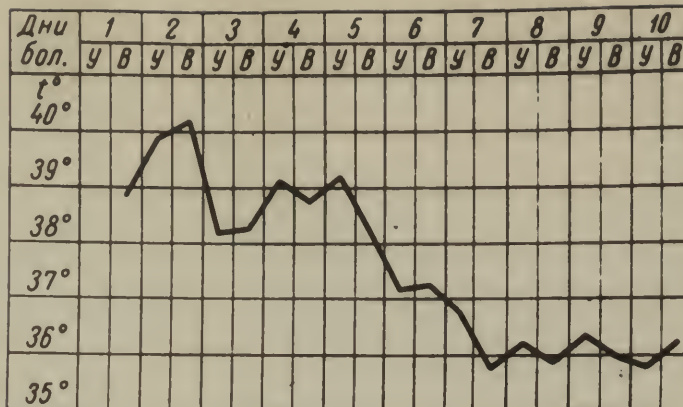
- a) one with a relapse of slight fever, and periodic exacerbations;
- b) one with occasional attacks of high temperature (1). The fever may also return a few hours before death (26).

CIGANKOV (33) distinguishes three types of fevers:

- 1) The first type reaches its maximum on the first day, continues at that height for 3-4 days, then it drops to normal in the next 2-3 days. The total febrile period is from 5 to 7 days.
- 2) The second type is similar to the first, but it lasts 5-6 days, and ends with lysis.
- 3) The third type, which occurs in 20 o/o of the cases runs the same as the others, but it ends with a critical fall of temperature on the 5.-6. day, remains normal for the 7th to 12th day, to rise again to subfebrile temperature

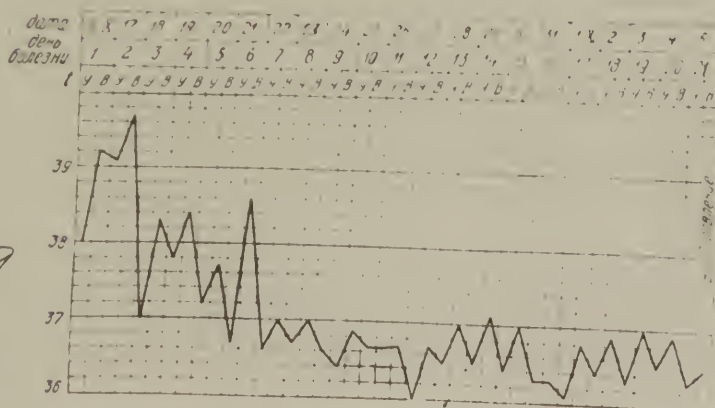
The type of fever may be modified by development of pseudo-uremia, meningitis, encephalitis, etc. (33).

Total duration of the fever is 7-12 days. At its end there may be a period of 3-4 days of subfebrility after the fall of temperature. The period of high fever is not coincident with the period of the greatest pathological damage (1). The stormy portion of the sickness is against an afebrile background: the violent hiccups, the multiple hemorrhages, the disorders of the cardiovascular system, the renal dysfunction, etc. (26).



FEVER CHARTS of epidemic hemorrhagic fever(upper, after CHURILOV A.V.,1941; lower, after REZNIKOV A.I.,1940) The top rubric of the lower chart shows the dates of months(from Oct. 16 to Nov.5)

(C.F.MAYER;Epidemic hemorrhagic fever)



Температурная кривая больного С. поступил 16.X, выписан 6.XII.1941

c) The pulse and respiration.

The pulse varies according to the blood pressure; when this is low, the pulse is weak. At-time of the critical fall of fever the pulse may become impalpable. With convalescence the intensity of the pulse returns to normal (1).

In mild cases, sometimes also in those of moderate severity, there may appear a r e l a t i v e b r a d y c a r d i a (42; 26), i. e., with a high temperature of 39° to 40° C the pulse remains just 90 to 100 per minute (25). Bradycardia with weak pulse was considered a valuable diagnostic sign at the early stage of EHF (36).

In the convalescent period an a b s o l u t e b r a d y c a r d i a is characteristic, with the pulse down to 40 to 60 a minute, usually connected with some lability (25; 33).

Tachycardia is the rule for serious cases, also sometimes for the end of the convalescent period (33). At the initial stage, a rapid pulse with a low blood pressure may be a sign of impending collapse (1). In very serious cases, v e n o u s p u l s a t i o n could also be detected (26).

d) The blood pressure.

In 21 o/o of the patients the arterial pressure, both systolic and diastolic, was lowered during the f i r s t s t a g e of EHF. In a good proportion of the cases it may remain lowered during the entire course of the disease so that there seems to be little correlation between the seriousness of the clinical course and the height of the blood pressure in EHF (25). In serious cases, there is a decrease in the systolic pressure at the time of crisis (1).

In the s e c o n d s t a g e of the disease the pressure becomes normal in 83 o/o of the cases, it remains lowered in 8.5 o/o and there may be a moderate increase in pressure in 8.5 o/o of the cases. The increase is usually in the diastolic pressure, e. g., 140 mmHg over 110 mmHg, and it is undoubtedly connected with the slight degree of azotemia of the post-febrile period.

In occasional cases with marked azotemia the systolic pressure may rise to 170 mmHg. With the decrease in azotemia and transition to convalescence the diastolic increase, also the systolic, disappears and it may give place to a slight h y p o t o n i a (26; 33).

e) The hemorrhagic diathesis.

The development of hemorrhagic diathesis in EHF can be seen usually in the s e c o n d s t a g e of the disease (25), but hemorrhagic spots may occur on the skin, the mucous membranes, the conjunctiva (1; 25), palate, buccal mucosa, pharynx, gingiva, with the 3rd day of sickness.

There are either small petechial spots, or streaks of extravasated blood (ecchymosis), or free bleeding through the various surface linings of the body (1). The petechial spots may be in the center of a hyperemic area, surrounded by congested small blood-vessels (1).

The ecchymoses may be in spots, patches, and stripes, usually at the region of the armpit (1; 26). Serious cases are marked by a strong tendency to profuse hemorrhages.

The site of hemorrhage may be located on the skin where the clothing is tight. Pressure upon the body may start hemorrhage in EHF, as shown by the so-called tourniquet test or RUMPEL-LEEDE phenomenon (15). Pinching of the skin may likewise provoke local bleeding (positive MOER sign; 25).

f) Vomiting, hematemesis and hemoptysis.

Nausea and vomiting are already noted at the o n s e t of the disease (1; 25) in about one third of the patients (25; 26). In the afebrile s e c o n d s t a g e, vomiting is a rule (25). It is of an indomitable character. First, it may be related to the meals, but later it will come without any extra provocation. In the seriously ill, it may contain blood (hematemesis).

The vomit is rather abundant, watery, frequently mixed with blood and bile. Its acidity may be 20, and it usually contains free hydrochloric acid so that persistent vomiting will result in great loss of chlorides in the body, and marked chloropenia (25). For this reason, test meals during the convalescent period may show a lowered amount of free HCl and an acidity of the gastric contents (25).

Serious cases may show blood in the sputum (1). The Russians observed hemoptysis in a few cases of EHF, and they remarked that the source of bleeding from the respiratory tract could not be detected by any means (percussion, auscultation, radiography) (25).

g) The skin.

Throughout the sickness the skin is dry. With the 2nd or 3rd day of disease there develops an especially marked hyperemia of the face and the upper half of the trunk. The hyperemia is of cyanotic color, or copper-red color, and may continue to exist for a few more days after the end of the febrile stage (25).

The skin of the 2nd stage is characterized by the appearance of multiple petechial bleeding, or purpuric eruption which is described later. In the 3rd stage of the disease the skin is pale, dry, with slight desquamation, especially noticeable on the face and chest (25).

There is no formation of visible or latent edema under the skin, and the McClure-Aldrich test will always give a normal absorption time (25; 29). There is a rather peculiar kind of 'mummification' in cases of intensive dehydration (26).

In 3 cases, REZNIKOV noted strong icterus of the skin and sclera (26). In the rest, a slight icteric tinge could be detected (26).

h) The skin rash.

There is no eruptive spotting on the skin in the first days (25; 26). The purpuric petechial rash is a form of the hemorrhagic tendency. It begins on the 3rd to 5th or 7th day, on the neck, shoulder girdle, axillary region, then it spreads to the upper half of the body (14). The majority of the patients develop such a rash by the 6th or 9th day. Postponement of the eruption until the 16th day was also noted (26).

The favorite sites of skin petechiae are: the lateral surface of the chest, the shoulder girdle, and the elbow (25; 26).

Though the skin petechiae are primarily small-spotted, they may change into striae or lines, or small groups. The individual elements of the petechial hemorrhage vary from dots to the size of soy beans (42).

The total number of petechial elements on the skin is very different. When there is an abundant crop, the rash may spread to the abdomen, lower extremity, and the neck. But in 75 o/o of the cases the petechial hemorrhages are not abundant (29). In rare cases they may cover the entire body (CHURILOV). There have also been some cases reported which did not have any rash (29).

My dear Mr. [Name],

I have just received your letter of the 15th inst.

and am glad to hear from you.

I am well and hope these few lines will find you the same.

I have not much news to write at present.

I am, dear Mr. [Name], very respectfully,
Your obedient servant,
[Signature]

At certain sites there may be found larger spots, so-called ecchymoses, of extravasated subcutaneous blood, sometimes among smaller spots of petechial bleeding.

The cutaneous hemorrhages may take 2-3 days for their full development. Afterwards they will last up to the 11th to 15th day of sickness in most patients. When the petechia are, however, not abundant and not marked they may disappear in 2-3 days (25).

Aside from the petechial purpuric spots, which are not correctly called a 'rash', there has also been observed a true rash, an eruption on the trunk which in its clinical form resembled the eruption of measles or the rash in urticaria (42).

i) The mouth and throat.

The throat and nasopharynx may be very red and congested (26) but there is no angina. The tongue is coated and striped (1). The oral mucosa is strongly hyperemic (36).

At the onset the tongue is dry and coated (25); in a few cases it is a typical strawberry tongue (42). The dryness of the mouth becomes especially marked in the second stage when it is a constant complaint of the sick, causing a sensation of intense thirst (26).

The soft palate, the palatal arch and the uvula are congested, and the soft palate may be covered with petechial spots. It was noted that such 'enanthemata' would sometimes precede the development of the cutaneous purpura.

Very small petechial spots are occasionally seen on the mucosa of the lower lip. The appearance of labial herpes was occasional (25).

After the onset of hemorrhages from the gums and from other parts of the oral mucosa there develops a very characteristic fetorexore, and the breath of the patient may smell like the odor of putrefying blood (25; 26).

k) The eye.

The condition of eyelids and conjunctiva was mentioned with the description of the characteristic face (see a) Face). Side by side with the hyperemia of the skin on the first day of sickness, there is congestion of the conjunctiva and sclera, which at the peak of the second stage (i.e., 7th to 10th day) may end in petechial or larger subconjunctival hemorrhages (42). Such hemorrhages may occur also in the retina (26).

The congestion of conjunctiva and sclera may bring about an appearance of 'rabbit's eye' (26)

4. Symptomatology of EHF by systems

a) The cardiovascular system.

The reaction of the cardiovascular system is generally revealed by the behavior of pulse and blood-pressure (quod vide).

At the first stage there is nothing abnormal on the heart, nothing at least that could be detected by auscultation or percussion (26). The heart's area is within normal limits, and the heartsounds are clear.

CHURILOV noted (1941) that there might sometimes be heard a systolic murmur over the mitral valve and that in single instances pericardial friction could be perceived (29).

At the end of the fever, i. e., in the second stage of the disease, the heartsounds are dull, muffled (33), and the heart seems to have a slightly enlarged area of percussion (25). This sign quickly goes, however, in the convalescent period.

b) The digestive system.

There is complete loss of appetite, sometimes amounting to a direct aversion to food (25). But in the convalescent period the appetite improves, except for some degree of 'pica' for acids and salts, and with some aversion to sweets (25) and tobacco (26).

Some cases were marked by right-sided subcostal pain at the onset of illness (25; 26). The abdomen is often inflated, meteoristic (26), very tender to palpation, especially in the ilcocecal region (26).

During the second stage, simultaneously with the appearance of lumbar pain, many patients complain of abdominal colic which is frequently localized around the umbilicus (25). Such colic has also been described in the first stage of EHF. In not a few cases the patients were admitted to the hospital with the diagnosis of acute abdomen, or acute appendicitis.

An immediate palpation of the abdomen would show that the typical muscular defense of appendicitis is missing in EHF (26).

There is some tendency to constipation in the

majority of cases (25; 26; 33). A few patients have diarrhea or enteritic stool on the 8th to 12th days of sickness (18 2 o/o). During the development of hemorrhages there may be observed free bleeding from the bowels, sometimes very abundant (25). This occurred, however, in serious cases only (42), but anywhere it may give rise to the false diagnosis of dysentery (26).

c) The uropoietic system.

The first stage of EHF has no particular sign of any deviation of the renal function from the normal. The urine (see later under Chapter IV: Clinical Pathology) assumes the character of urine in fever.

In the second stage which begins between the 3rd and the 7th or 9th day of illness, there develops the characteristic urinary symptoms of the typical renal lesion of EHF which dominate the rest of the clinical course of the disease. These symptoms usually appear at the exact end of fever (25) but the renal trouble may already become manifest on the 3rd day of illness, rarely a day or two after the cessation of fever (25; 26).

The characteristic changes in the urine are described in the next chapter. The symptoms vary according to the degree of organic changes in the kidney (9). Apparently, the height of the sickness is coincident with the full development of renal dysfunction (1). There may be oliguria, in serious cases even anuria (1; 25), later changing to polyuria.

Albuminuria may be present in traces, or in large measurable amounts. There are also various pathological elements to be found in the urine and the urinary sediment (See in next chapter; 25).

In the third stage, the urinary symptoms still predominate, but the oliguria changes gradually to polyuria, with polyakisuria, nycturia, thirst, polydypsia which will finally disappear in the 3rd or 4th week of the disease (25).

According to the concentration-dilution tests the renal function is still ineffective on the 3rd week of sickness. By the 4th week, in a few patients the kidney regains its power to concentrate the urine up to a specific weight of 1021, but the majority of patients who were said to be in good physical condition in their convalescence and who did not have any further subjective complaints still kept on secreting urine of 1012 to 1016 specific weight (25; 26).

d) The liver and the metabolism.

- There was some evidence of functional disorders of the liver (1). At palpation the liver was sometimes soft and painful, though it is impalpable in most patients (42). But for three to ten days after the cessation of fever it may be slightly enlarged (25; 26; 33)

The amount of reduced v i t a m i n C in the blood was found diminished, and there seemed to be also a loss in the capacity of the body to retain ascorbic acid even when it was given in surplus doses (1). STERGEEVA and ROMICHEVA also observed that vitamin C was lowered in the blood at all stages of the disease (29).

The renal lesions of the second stage are accompanied by a z o t e m i a which then becomes responsible for the development of ordinary uremic symptoms such as nausea, vomiting, hiccup, etc. (25). Out of 22 Russian patients only one, who died later, had a strongly marked azotemic uremia (26).

e) The toxemia and the nervous system.

The toxemic condition is manifested in EHF by severe headache, lumbago, lack of appetite, nausea, unpleasant dry throat, and insomnia. These complaints often appear at the onset (1). They are most severe at the height of fever, and they disappear when the temperature returns to normal (1). The febrile period may also be marked by giddiness, and general weakness as the result of toxemia (25).

Pathological symptoms of neural origin may be observed in all phases of EHF. They are, however, always fugitive, according to the progress of recovery (25).

The cerebral symptoms are comparatively few (6). Part of them can be explained by the relatively large hemorrhages in the diencephalon (6). There may be temporary m y o p i a (for 1-3 days), v e r t i g o, and hiccups (1). These symptoms are sometimes very much pronounced, almost suggesting a toxi-infectious e n c e p h a l i t i s (26). - Even paresis of the f a c i a l n e r v e was mentioned (33).

The s e n s o r i u m remains clear in most cases. There is a peculiar e u p h o r i a, in spite of the seriousness of the condition (26). In two instances (9.1 o/o of a series) d e l i r i u m developed, with twitching of the facial muscles, general excitation, coma, and subnormal temperature, ending in death (26).

The temporary myopia may be of high grade, but it occurs only in the more serious cases (1). At the beginning of the afebrile period

some patients complained also of other visual disorders such as fogged vision, etc. The eye fundus, however, was normal, except for a few retinal hemorrhages in some cases (25; 26), or for a transient hyperemia of the optic papilla (BOIKOV; 29).

Hiccup is a rather late symptom. It occurs mostly (86.4%) on the 7th to 10th day of illness; it may also develop later (26). If it is an obstinate one it should be taken as a bad prognostic sign (1). Its cause is some degree of azotemia. It may become continuous and very unbearable in its strength (25). Hiccup is less frequent in its appearance than vomiting. Its rate may reach 7 a minute (29), or even 20 to 30 a minute (30).

In the first stage there may also be inhibition, sluggishness, and somnolence (25). Headache, sometimes very strong, appears in all. Many patients may show signs of meningism: Kernig sign (31.8%), or rigidity of the occipital muscles (63.6% by one source; less frequent by another) (25; 26). There is a high degree of weakness of a musculo-neural character, neuralgias of varying location, gastroenteralgia, etc. (26).

The symptoms of the first stage persevere during the second period, in spite of the cessation of fever. They may become more marked as the azotemia increases. Frequently insomnia develops owing to the lumbar pain, abdominal colic, vomiting and hiccup.

In a few single cases the physiological tendon reflexes were increased, or decreased in intensity; sometimes they showed irregularity on both sides (36). Various pathological reflexes (Babinski, Rossolimo, Oppenheim, etc.) were occasionally also observed. Infrequently there was anisocoria, miosis (25; 26).

Cutaneous hyperesthesia at the lumbar region and in the hypogastrium was a frequent sign (25; 26).

During the first days of illness, the majority of patients exhibited a white dermographism (25), which changed to red in the second stage of EHF, sometimes assuming an urticarial character. In the convalescence it might disappear (25).

f) The respiratory system.

Nosebleed may occur at any period of EHF (25), but ONO has seen it only in serious cases (42). The respiratory passages are free from catarrhal symptoms. There is no introductory common cold, though swelling of the nasal mucosa occurs not infrequently.

Diffuse bronchitis was noted in one third of the cases (25; 26), and bronchopneumonia in a few. (For Hemoptoe see p.30)

g) The spleen and the lymphatic system.

The spleen may be of solid consistency, tender on palpation (25), though it is mostly impalpable (42; 26). Splenomegaly was noted only in cases of mixed infection (1).

The lymphatic system appeared to the clinician without perceptible changes (25), and the lymph nodes were not found enlarged (26).

5. Complications and sequelae of EHF.

The Russian patients who were described in 1940 by ROTENBURG did not have many complications. Unilateral p a r o t i t i s was seen in two, one requiring surgical treatment. A few patients suffered from f u r u n c u l o s i s (25). CIGANKOV also commented on parotitis, putting its frequency at 3.4^o/o (33).

Japanese authors mentioned hemorrhagic p n e u m o n i a , and catarrhal e n t e r i t i s among the complications of EHF (6).

The hemorrhages themselves which occur in this infectious febrile disease should not be labelled complications since they belong to the basic clinical picture of the disease (25).

Recent U.S. Army experience indicates that, so far, there are no residual effects of EHF. This has to be further investigated, however (15), especially in view of the experience of the Russians.

Transition of EHF into a chronic condition was not seen in the Russian Far-East, at least not in the cases described by ROTENBURG in 1940 (25), though there was always some functional disorder left in the kidney as was shown by the incomplete concentrating capacity of the kidney in patients at their discharge from the hospital in the 4th - 5th week of the sickness (25).

In 1941 CHURILOV also stated that EHF does not end in a chronic renal disease (29). During his 5-year study of the infection (--which he had known as hemorrhagic nephroso-nephritis--) he never saw a true case of uremia, and observed only ten cases of a pseudo-uremic condition (29).

6. Prognosis of EHF.

Early Russian investigators considered in 1940 that the prognosis is always doubtful (26). But as early as the next year CHURILOV remarked that the overwhelming majority of the cases had a

favorable outcome (29; 30). Persons examined at later admissions to hospitals, a few years after their recovery from EHF, were found without any renal disorder (30).

According to the Japanese the outcome of EHF depends upon the strength of the heart, whether it can withstand general toxemia, fever, albuminuria, hemorrhagic diathesis, and the hiccups. One has always to look out for possible r e l a p s e s, or for the development of general weakness (1). As a practical example of the regular outcome of the disease, a small epidemic can be mentioned comprising 24 cases in a Japanese Army unit; 20 of the patients exhibited a light course of EHF (36).

Poor is the prognosis when any of the following signs is present: 1) collapse in the initial stage, with rapid pulse and low blood pressure, 2) vomiting, with residual contents, 3) obstinate hiccup, 4) marked albuminuria, with possible anuria, 5) severe cerebral symptoms, 6) increase in the tendency to hemorrhages, 7) profuse hemorrhages, 8) marked, high leukocytosis, 9) high grade myopia (1).

7. The mortality of EHF.

This subsection cannot be anything but the enumeration of death rates in the various observed epidemics.

In the 1938-39 epidemic in the Primorskaya, REZNIKOV lost 7 out of 22 cases (31.8% fatality rate). Death came on the 7th to 21st day of illness. In ROTENBURG's series from Far-Eastern Russia the mortality of epidemic hemorrhagic fever was between 5% and 10% (25). He expressed his hope that with an early hospitalization and energetic treatment a reduction of the death rate might be possible.

The Japanese statistics recorded an epidemic of the disease in 1941, with 32 persons sick, 5 of whom died. In 1942 another epidemic produced 77 sick, some of whom died (perhaps from another infection) (1). At Sung-wu, in the 1939 epidemic six died out of 20, and in the 1941 epidemic 26 died out of 236 (39).

There was no death observed during the outbreak of EHF in Heian Province in 1941 (7). In the Korin epidemic of 1942, 15 out of 102 patients died (14.7% fatality rate) (39). In a small outbreak at Tungning, two died out of 17 true cases of EHF and 7 suspects (36).

The 1946 U.S. Government pamphlets reported the mortality as high as from 20% to 50%, with additional rates at from 5% to 20% (13), and at 13% to 36% (14). In the recent report of TAKAMI (39) the death rate of EHF was given at 13.2%.

TERSKIN reported a mortality of 10 o/o (31). ABRIKOSOV gives the fatality rate as from 3 o/o to 5 o/o (24). Also in the cases treated by Russians, the mortality of EHF varied from 2 o/o to 6 o/o. In the Khabarovsk epidemic it was 5 o/o to 6 o/o, in Blagoveshchensk (almost opposite to the Manchurian Heiho) it was - from 2 o/o to 3 o/o, and in CHURILOV's series it was 3.3 o/o (29).

The mortality rate of the 1950-51 cases observed in U. N. troops was reported at 13.3 o/o (based upon 25 deaths out of a total of 196 definitely diagnosed cases) (15; 20).

The mortality rate depends in some respect upon the age of the patient. On one hand an old coolie may die after an exhaustively long course of EHF while a 19 yr old youth may recover quickly on the 4th day (7). On the other hand, one source reported that most of the fatal cases were in quite young people, of average body constitution and average nutritional status (4).

The death rate also depends upon the virulence of the virus and the epidemic, as well as the incidental treatment. Japanese authors observed that the death rate may be lower and higher, sometimes up to 20 o/o-30 o/o (34), with an average of 15 o/o (1; 34). Most of the fatal cases have occurred at the beginning of the epidemic outbreak (1; 34). The mortality rate was generally higher in the autumnal outbreaks (TAKAMI; 39).

Death is rarely sudden, and rarely in the first days of the disease (14). It occurred on the 6th-7th day in 20 o/o of the deceased, on the 8th-to 12th day in 50 o/o, and on the 22nd to 30th day in 30 o/o (28).

The cause of death is mostly a result of the renal lesion (40), or some intercurrent disease (28). In REZNIKOV's statistics, death was due to heart failure and general toxicosis in 42.8 o/o, to complicating infection in 14.3 o/o, to general sepsis in 28.6 o/o, to azotemic uremia in 14.3 o/o.

Peritonitis and bilateral pneumonia were also recorded for causes of death (28; 29).

As a rule the patient's body at death is strongly emaciated, almost 'dried up' (26; 28). According to LEIBIN, in death from EHF the cadaveric signs appeared very quickly (28).

CHAPTER V

CLINICAL PATHOLOGY

1. The blood picture of EHF.

The blood picture varies according to the stages of the disease. At the onset there is erythrocytosis, with appearance of erythroblasts. The hemoglobin count varies with the red-cell count. There may be leukopenia (26) followed in severe cases by marked leukocytosis, sometimes up to 80,000 cells per mm³.

After the crisis, the blood-cell values return to normal in from 1 to 10 days' time (1). In convalescence, there is leukopenia, with relative lymphocytosis (1; 25).

The serious cases show an extreme shift to the left in the blood picture, with the appearance of myelocytes (-- in 64.5 c/o of the cases of DUNIEVSKY; 27--), and without lymphopenia. Other sources reported eosinophilia at all stages, and plasmocytosis in convalescence. ROTENBURG found that initial eosinophilia is rare, but there were many patients (82.7 c/o of all) with Türk type of irritation cells (25; 27). The monocytes were often reduced (26).

There is disturbance in the thrombocytic count,-- with various disorders in the formation of megakaryocytes (1; 25). The thrombocytic count gives low values in the first stages of illness (87,000 to 120,000 in some Russian material) (25; 26; 29). The count of thrombocytes is in indirect relation to the severity of the clinical course. It may be reduced on the third day of disease to 87,000 and increased again to 140,000 on the 7th day, to 180,000 on the 10th day, to 200,000 on the 14th day of the disease (29).

The hemoglobin was between 85 o/o and 100 o/o during the first 6-8 days of illness (25). After the vomitings, and during improvement it was less. At recovery the Hb percentage increased. Sometimes, the rise in Hb went parallel with the increase in proteinuria (26).

The erythrocytes were between 4.5 and 5.5 millions per mm³. After vomitings, the red-cells decreased to 3.6 millions or 4.5 millions. With recovery they again increased. Poikilocytosis was also noted (26). The color index was usually around the unit, or slightly below one. The reticulocytes were normal in count.

The blood sedimentation rate was relatively slowed down (2 to 10 mm per hour) in 26 o/o of the patients—during the first stage of the disease; it was up to 30 mm/hr in 43.5 o/o, and still quicker in 30.5 o/o (33). In the second stage, 57.1 o/o of the patients had a sedimentation rate of 30 mm/hr, and another 35.8 o/o had it at a still quicker rate (30 mm/hr to 50 mm/hr. The sedimentation rate returned to normal during the 4th week of illness (25; 26).

2. The blood chemistry of EHF.

A few biochemical data on EHF were collected by Russian scientists (25). As a rule, there were significant changes in the chemical components of the blood from the beginning of the second stage.

The majority exhibited hypochloremia (320 to 360mg o/o in whole blood; rarely 257mg o/o), though, after the period of vomiting, the blood chloride level quickly returned to normal, usually in the second week of sickness.

All patients have azotemia in the second period. From the 4th or 5th day on, the residual nitrogen increases to an average of from 100 to 150mg o/o, rarely to 200mg o/o (25), or even 300mg o/o (26). Moderate increase in nitrogen may return to normal at the end of the 3rd or at the beginning of the 4th week. Thus, the recovery of normal nitrogen values is slower than the chloride recovery. When these values are put on the same chart, a typical curve results, which shows that the azotemia of EHF is a chloroprive azotemia (ROTENBURG; 25).

The bilirubin level was found normal in 4 patients who were tested on the 6th to the 16th days of sickness—(25). The Van den Bergh test is always indirect in all cases (33).

Blood sugar was measured in 6 patients on the 6th to the 17th days. It varied from 65mg o/o to 100mg o/o.

Blood calcium values were from 8.4mg o/o to 11.2mg o/o (5 patients; 4th to 16th day)

The reserve alkalinity was determined in one patient on the 9th day of sickness, when it was 35.4 o/o by volume, and on the 16th day, when it was 44.7 o/o by volume.

Japanese observers stated that the A/G ratio is usually normal, and fibrinogen remains normal. The blood protein is reduced, but it will increase during recovery.

The coagulation time varies from day to day. It may be 6 min. 15 sec. on the 3rd day, 3' 45" on the 7th day, 2' 50" on the 10th day, etc. (29).

The bleeding time is gradually prolonged as the disease progresses to convalescence. It may be 4' 25" on the 3rd day, 3' 30" on the 7th day, 4' on the 10th day, 6' 45" on the 14th day, and 8' 25" on the 16th day, though the number of thrombocytes is increasing (29).

3. The cerebrospinal fluid of EHF.

The cerebrospinal fluid remains clear, and under normal pressure (26), even with cerebral symptoms. The pressure may sometimes rise to 200-300mmHg. Tendency to xanthochromia was observed (39). In some cases, the spinal fluid contained 537 to 725mg % of chlorides (25). The Nonne-Apelt and the Pandy tests were found positive by REZNIKOV (26). The Takata-Ara test is mostly positive during the peak of the fever (39).

4. Electrocardiography in EHF.

The electrocardiogram, when taken after the crisis, gives a graph which is interpreted as a fair indication of myocardial degeneration (1).

It shows change not only in the heart muscle but also in the conductive system. In the first stage, many patients show lowered voltage of R in leads I and II, absence of PQST, splitting of R in leads I and II, prolongation of R in leads I and II. During convalescence there appear certain changes such as absence of PQST in lead II, slurring of T in lead III (33).

5. The urine in EHF.

In the first stage of EHF the urine assumes the character which is usual in all febrile diseases: - it is highly concentrated, and it has a high specific weight (25).

In the second stage, as the renal lesions develop between the 3rd and 7th day of illness, the urine becomes turbid, diminishes in its daily amount, and shows high concentration. For a few days its specific weight may remain 1020 to 1030, then it quickly drops to 1002 to 1010, and remains low throughout the next few weeks (25). Oliguria may change to full anuria for 1 to 3 days (25).

Simultaneously with the oliguria the protein content of the urine increases rapidly; then it quickly decreases again, and usually in the third week of illness the proteinuria is almost negligible in all patients.

In ROTENBURG's series the maximal amount of urinary protein was 33 per mille (25); mostly it moved between 3 and 6 per mille; rarely, it was less. Japanese sources indicate that at the time of the critical change in temperature the albuminuria may reach the amount of 50 per mille in the more serious cases (1; 26).

Variation of albuminuria may be shown by the following clinical example of DUNIEVSKY (27): 3rd day, no protein in urine; 4th day, 0.03 per mille; 6th day, 6 per mille; 7th day, 6 per mille; 11th day, traces of protein. Another more striking example is the following: 5th day, traces of protein; 6th day, 24 per mille; 7th day, 12 per mille; 10th day, 0.09 per mille.

The proteinuria is not over 1 per mille in 81.6 o/o of the patients, it is between 1 and 3 per mille in 5.6 o/o of the cases, it is between 3 and 10.4 per mille in the rest of the patients according to a Russian observation (33). In special cases it may be over 10 per mille.

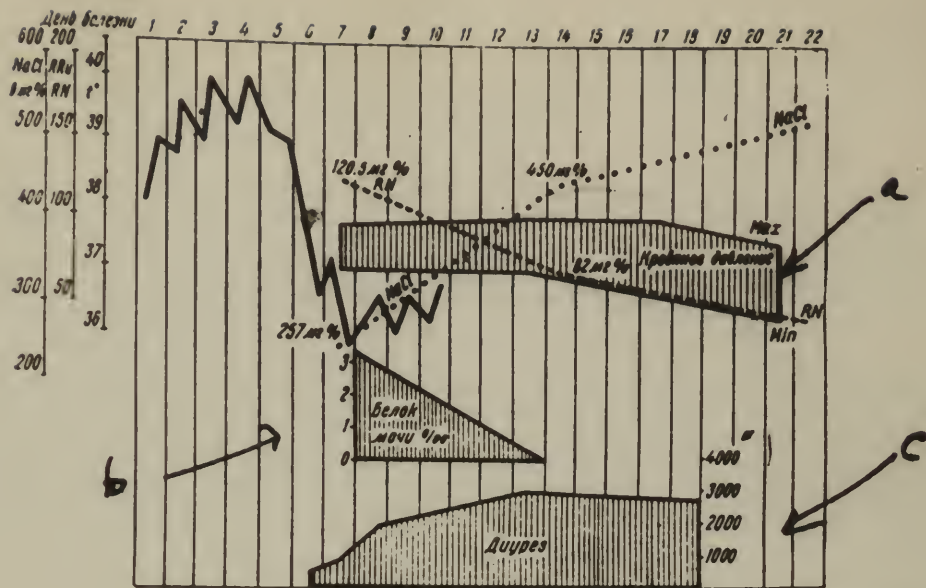
When the urine appears protein free there may still be a latent (or microscopic) hematuria (1). There is no case without some degree of hematuria (25), though the urine becomes visibly bloody only in the more serious cases (1). The urine of the severely ill may also contain some fibrin clots (1).

In 12 cases of a series (or in 9.6 o/o) the fall of temperature was followed by transient glycosuria for a few days (33). Test for diazo, urobilin, urobilinogen and indican gave no definite results (42).

The urinary sediment had hyalin and granular casts in all patients (others reported them in 50 o/o of the cases; 33). ROTENBURG found wax casts and renal epithelial cells in 50 o/o of the patients, together with leukocytes and erythrocytes which were present in varying amount (26). There seemed to be no correlation between the richness of urine in formed pathological elements and the degree of proteinuria (25).

In the third stage of EHF, as the condition of the kidneys and the general status of the sick improve the amount of urine increases and the oliguria or anuria of the second stage is followed by polyuria within a few days.

The daily frequency of urination becomes 10 to 20, with signs of nocturnal frequency (25). This is usually connected with dryness



FEVER CHARTS in epidemic hemorrhagic fever, with variations of other factors(after S.S.ROTENBURG, 1940)

1)Area a :Variation of blood pressure in mmHg; top edge for systolic(Max), lower edge for diastolic(Min)

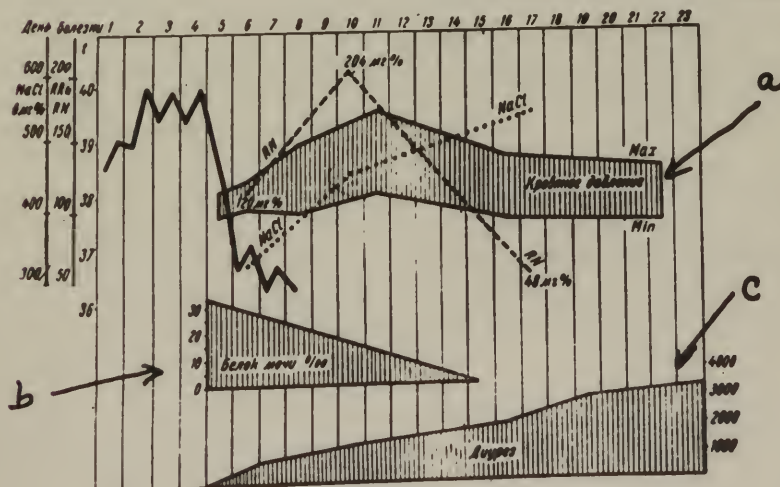
2)Area b : Graph of proteinuria expressed in g/1000 ratio

3) Area c : Diuresis in ml.

RN: graph of residual nitrogen in mg%

NaCl: chloremia graph

(C.F.MAYER;Epidemic hemorrhagic fever)



of the mouth and thirst for 5 to 10 days. Certain patients have consumed from 3 to 5 quarts of water daily (25). For this reason LEIBIN speaks of a *d i a b e t e s i n s i p i d u s* symptom complex in EHF (28), considering the polyuria, the low specific gravity of the urine, and the polydipsia.

Great emphasis is laid by DUNAEVSKY upon the presence of the so-called *f i b r i n c a s t s* in the urine. Such casts have already been described and illustrated by NEIER in his Atlas published in 1887 (*Atlas mikroskopii krovi*, etc.; I was unable to find a copy of this atlas).

The fibrin casts are very long, seen to cross the entire field of vision at low magnification under the microscope. They appear and increase in number concurrently with the albuminuria, but they are abundant also in the protein free urine for several days, sometimes for 10 days after the urine becomes free of albumin (27).

CHAPTER VI

DIAGNOSIS OF EPIDEMIC HEMORRHAGIC FEVER

The diagnosis is based upon the presence of hemorrhage, the RUMPEL-LEEDE phenomenon (which may be positive for 2-3 days only or throughout the entire disease), the MOSER pinching test, the determination of bleeding time and coagulation time, and the thrombocyte count, but, most of all, upon the characteristic clinical symptoms of the disease.

In the early stage the characteristic features are: the onset of fever with chills, the flushing of the face ('pseudo-suntan'), the congestion of the bulbar conjunctiva ('rabbity eyes'), soft pulse, and nausea (1). Relatively early are the symptoms of hemorrhagic diathesis, the petechial spots and the ecchymoses, the albuminuria, erythremia, and eosinophilia (1). Somewhat later the signs of general toxemia develop, together with leukocytosis, perhaps visual disorders, hiccup, and a positive NAGAYAMA test in the urine (See below under: urine) (1).

Other typical symptoms which are useful in diagnosis and differential diagnosis are: the typical fever chart, the constant and strong headache localized in the forehead and/or the occiput, vomiting and nausea, epistaxis, a b s e n c e o f e d e m a of the subcutis, increased dehydration with emaciation of tissues, and the typical disorder in diuresis.

A practical urinary test was described by Col. NAGAYAMA, of the Japanese Army, for the detection of *f i b r i n u r i a*. The

test may be performed so that drops of the patient's blood are introduced into his voided urine; when the blood does not mix with the urine but stays suspended it may be assumed that there is fibrin in the urine (1) (Note; I report this test without any critical comment).

1. Serological tests.

In the course of research on the etiology of EHF, various types of serological tests were performed with the patients' blood, most of them giving negative results.

The agglutination and the complement fixations tests with a number of antigens (leptospiral, Salmonella typhi and paratyphi A & B) were negative (25; 30; 31). The complement fixation test for syphilis was found weakly positive in some Japanese patients (39) suffering from EHF.

The Weil-Felix test also gave negative results (1). (This is contrary to the report in the 1946 U.S. pamphlets which stated that the Weil-Felix test, with unknown antigen and unknown titer, was positive; 13; 14). The test was negative with such antigens as Proteus OX₁₉, OXK, and OX₂ (25; 30; 31).

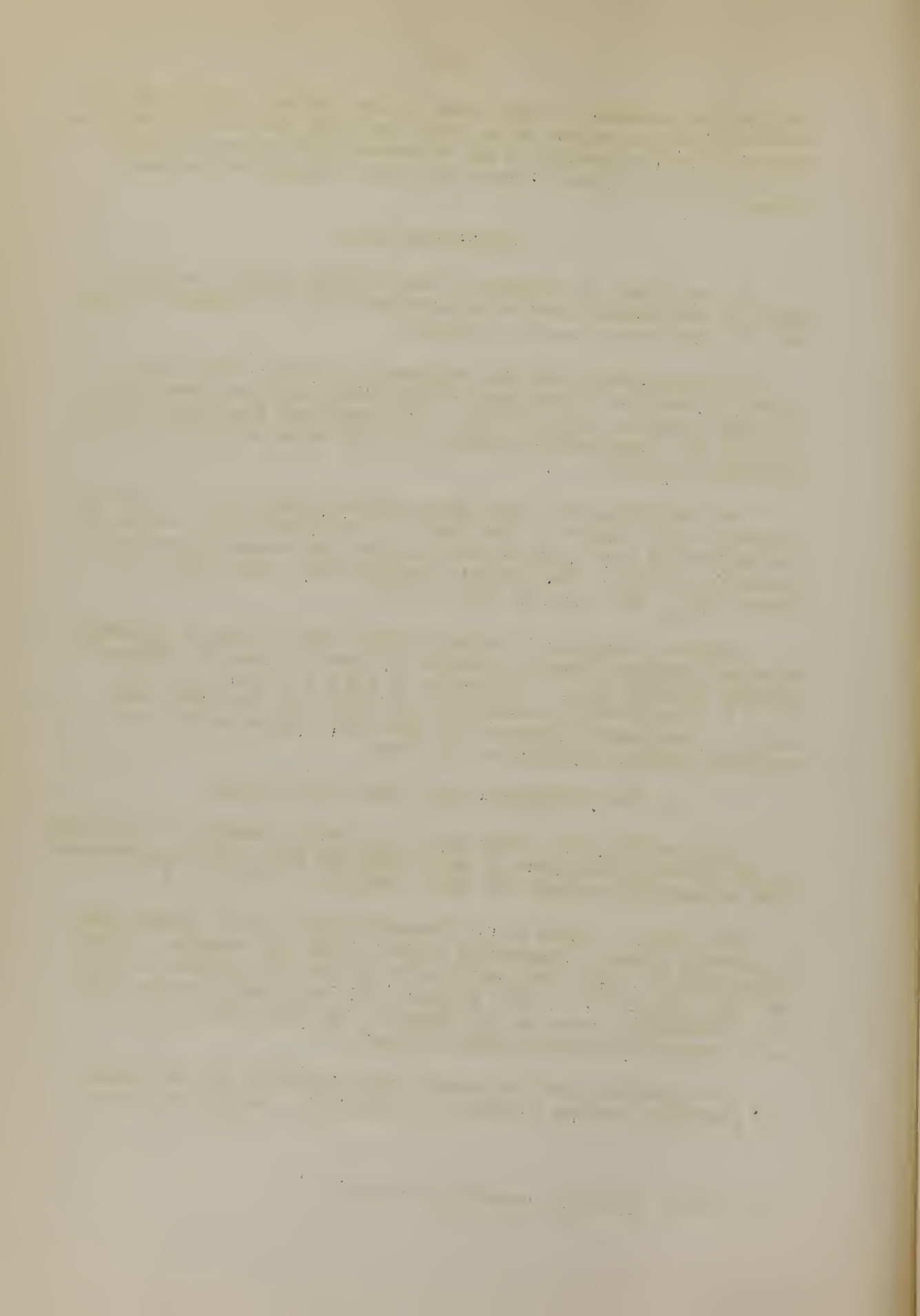
Specific serological tests for EHF, with the use of antigenic material prepared from the viscera of those who died of EHF were studied by IKEDA (41). A specific p r e c i p i t a t i o n t e s t gave positive results in only 50% of the sick, however. A complement fixation test with EHF antigen would give positive results in 100% of the sick.

2. The biological test (skin test) of EHF.

A biological test based upon the allergic reaction of the skin in EHF has been described by Mituo IKEDA in 1946 (41) (For preparation of specific antigen see under Immunity, in Chapter X).

The test was tried out in November 1942, and in January 1943 at certain places in Manchuria where the EHF was endemic. IKEDA found that his test gave positive results in all 7 cases of typical EHF, and in all 7 other patients who had already passed into the convalescent stage of the disease. In other words, his tests seemed to respond without failure.

The positive reaction appears from the first day of disease and gradually becomes stronger in positivity. During the first



stage, there is also swelling and induration around the site of the antigen injection. Even six months after sickness the patient will react with clearly visible hyperemic area to the test (41) (For its full description see Chapter X)

Specificity of the test is shown by the fact that no positive reaction was obtained in patients who were suffering from eruptive typhus, scarlatina, recurrent fever, typhoid fever, pulmonary tuberculosis, bronchitis or plague (both types). The skin test did not infect the tested persons with the virus of EHF as IKEDA assures us (41).

3. The differential diagnosis of EHF.

EHF has been treated under all sorts of labels in Manchuria (1). In unrecognized cases it was recorded by the doctors as acute hemorrhagic nephritis (25), war nephritis (32), atypical scarlet fever, toxic infection, electric-shock type, exanthematic typhus, Werlhof's purpura, leukemia, sepsis, hemorrhagic pneumonia, typhoid fever, toxic influenza (25), even ordinary scarlet fever (1).

We have seen that Chinese doctors registered it as a form of 'syphilis' (1), while others diagnosed it as a case of sunstroke (1).

The most likely mistake in diagnosis is when EHF is recognized as purpura, especially anaphylactoid purpura (1). This error can mostly be avoided by the proper education and information of the physician. The great resemblance of EHF to other forms of purpura (23) is to be kept always in mind. The German Red Cross Expedition to the Russo-Japanese War in 1904-05 found various forms of hemorrhagic diathesis among the fighters in Manchuria. Some of them were light cases, some of them were more severe, but, as the report stated, a differential diagnosis was extremely difficult.

SNAPPER stated that in Peiping all kinds of hemorrhagic diathesis are frequently encountered, and one has to be always alert not to err in the differential diagnosis of these affections (78). This may be true for the entire Far-East since the occurrence of thrombocytopenic purpura or hemorrhagic diathesis of other pathogenesis is rather common in infectious disease such as typhus fever, relapsing fever, and even typhoid fever.

The diseases which need differentiation from epidemic hemorrhagic fever are the following: scurvy (31), all types of purpura in-

cluding the anaphylactoid type, the simple, rheumatic, abdominal, and the Henoch type as well as the hemorrhagic capillary toxicosis (25), electric injury resulting in purpura, smallpox purpura, scarlatinal and septic purpura, relapsing fever, epidemic cerebrospinal meningitis, gastric ulcer (26), malaria (26), appendicitis and appendicitic peritonitis (26), aleukia hemorrhagica, hemophilia and hereditary thrombasthenia, pseudohemophilia hepatica (1), food poisoning (13), paratyphoid fever (25; 26), plague (13), and dysentery (26).

The differentiation of epidemic hemorrhagic fever from a) leptospirasis, b) Koshan disease, c) Manchurian typhus, and d) the other Soviet-Russian forms of 'epidemic hemorrhagic fever' is discussed in the following sections.

a) Differentiation from leptospirasis.

Serological tests with *Leptospira* antigens invariably give negative results (NARCISSOV; SHUBLADZE; KHOREIDZE; 25).

In 1941 TERSKIH compared the frequency of clinical symptoms which occur in both leptospirasis and EHF, and came to the following table:

	EHF	LEPTOSPIRASIS
recurrent fever	1.6 o/o	26 o/o
petechial rash	80 o/o	1 o/o(less)
linear rash	often	none
maculopapular rash	none	50 o/o
herpes labialis	none(?)	11 o/o
hemorrh. diathes.	yes	no
liver enlarged	sometimes	sometimes
spleen-enlarged	sometimes	sometimes
suppur. meningitis	none	8 o/o
meningism -	8 o/o	28 o/o
postinfect. psychos.	yes	yes
uveitis	none	4 o/o
parotitis	yes	no
Residual N	200mg o/o	60mg o/o
shift to left	myelocytes	juvenile
leukocytosis	rare	50 o/o
thrombocytes	60-90,000	160,000
sedim. rate	40mm/hr	40mm/hr
proteinuria	strong	moderate -
time	all year	June-Sept.
vector	rodents	rivers
mortality -	10 o/o	none
microsc. bact.	none	<i>Leptospira</i> in blood
serology	?	leptospirin

Hence, one of the acute infectious diseases which has to be ruled out in the diagnosis of EHF is leptospirosis, especially its special form called leptospirosis grippo-typhosa (water fever, harvest fever) which has been observed in various parts of the Soviet Union since about 1923.

(To be printed fully in the final edition)

b) The differentiation from Koshan disease.

Another disease of obscure origin which needs differentiation from epidemic hemorrhagic fever is the endemic ailment found in Manchuria, especially in the provinces of Lunkiang, Pinkiang, Chientao and Jehol. It was discovered in the fall of 1935, and is called by the town where it was first seen, the K o s h a n (or kushan, or kokushan) disease.

The basic lesion of this ailment is degeneration of the myocardium (51; 52; 55) with cell infiltration, a chronic heart failure due to fibrotic myocarditis. In addition there are various other pathological changes which are common with those of EHF and may cause some confusion or difficulty in diagnosis. Congestion of various viscera, and hemorrhagic spots on the visceral surfaces are also observed (45).

(Full description to be printed in the final edition)

c) Differentiation from Manchurian typhus.

(To be printed in the final edition)

d) The other types of Soviet-Russian EHF.

As far as differential diagnosis is concerned one should keep in mind that at various points of the Soviet Union, aside from the Far-East, obscure fevers have been described during the last decade, all of which have h e m o r r h a g i c d i a t h e s i s with fever as their main symptoms.

In the Russian literature these are the diseases which are called epidemic hemorrhagic fever, or acute infectious hemorrhagic capillary toxicosis, sometimes with a place name added as epitheton ornans, while the Far-Eastern type of endemic disease which the Japanese have officially named epidemic hemorrhagic fever has been treated in the Russian literature as the 'so-called infectious (or hemorrhagic) nephroso-nephritis.

At present I do not want to analyse these Russian reports in any great detail, it is only the most essential differences between these various geographical types of infectious capillary toxicosis and EHF which are briefly stated here for the facilitation of differential diagnosis. One should keep in mind that purpura is a general form of reaction of the organism, and its symptomatology is always similar in quality.

1. The Tashkent h e m o r r h a g i c e d e m a (57). In their Hematology (1948) KASSIRSKY and ALEXEEV described a form of hemorrhagic diathesis of infectious origin (SMORODINCEV) which first occurred during the 1941-45 Russo-German War. It was marked by hemorrhagic spots and edema on the lower-extremity. It was detected in Tashkent, and the Moskva District. Whether it is due to a virus invasion remains as a problem of future research.

2. The U z b e k i s t a n infectious hemorrhagic fever (58; 59). The first cases of the fever were described in 1927 in Stalinabad by M. V. VOINO-J' SENECKY and J. V. POLONSKY. In 1941 SIPOVSKI published his observations on 18 cases of 'acute diapedetic hemorrhage' from the gastrointestinal tract. In the same year, in Termez, another Uzbekistan town, similar fever with enteral bleeding was observed by SEMJ' TOVSKAJ' and SIDTDYKOVA. Their later cases were reported in 1950 (59). Its mortality was 100 o/o. There was moderate bleeding in all internal organs, and free blood in the stomach.

(To be printed fully in the final edition)

3. The O m s k hemorrhagic fever (60). This form of infectious hemorrhagic diathesis resembles septic angina. It shows a typical

leukopenia in the peripheral blood, and myeloid reaction in the bone marrow (KLEIN). There are also changes in the central nervous system. It was stated that analogous phenomena occur in the next form of capillary toxicosis.

4. The Crimean hemorrhagic fever (61 to 66). This form is also known as 'the so-called acute infectious capillary toxicosis' (KOLACHEV). It was observed first in 1944-46 in the harvest fields of the Crimean District. It was believed that the virus was carried by *Hyalomma marginatum* and its nymphs.

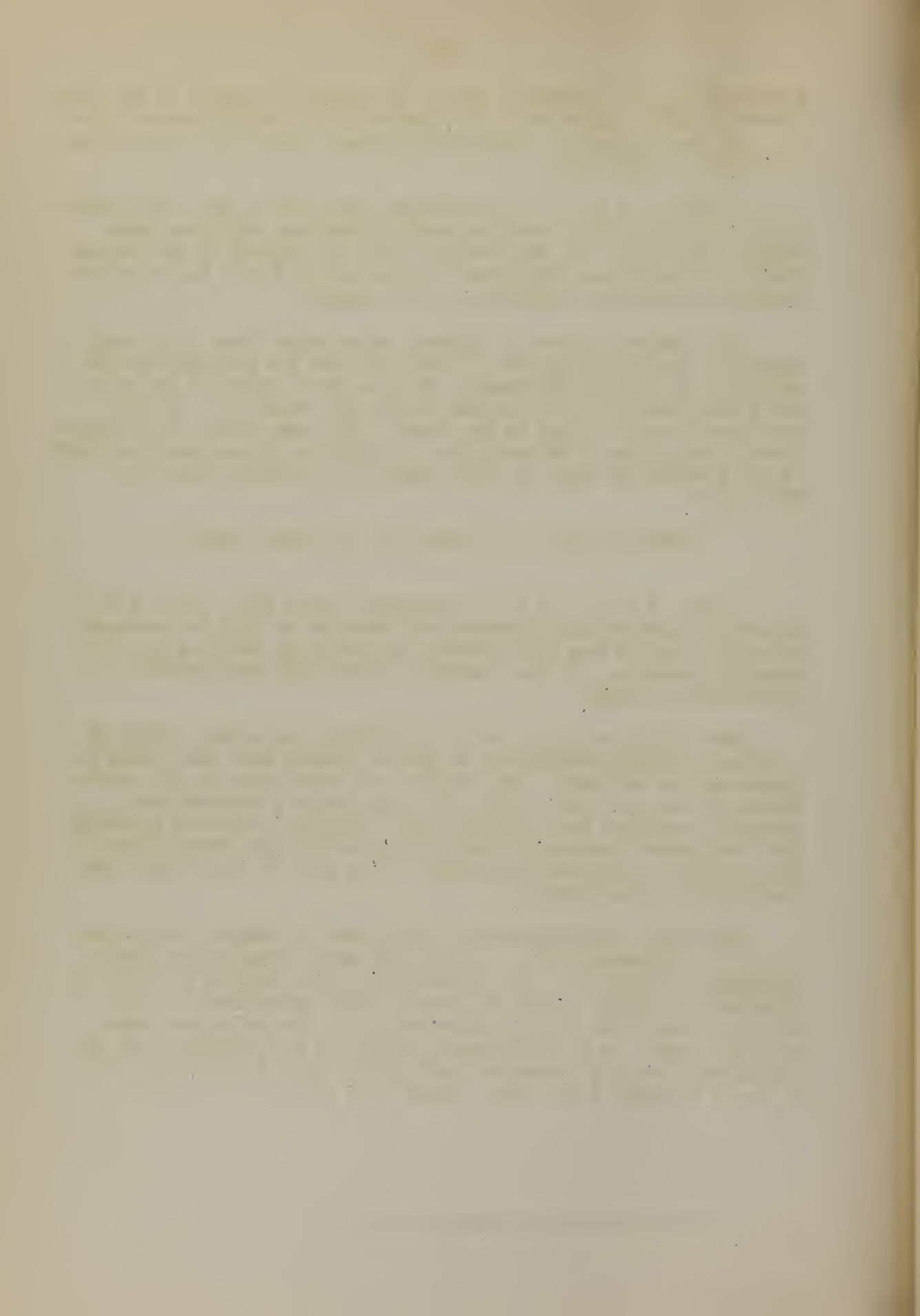
The clinical picture of Crimean hemorrhagic fever is in many symptoms identical with that of EHF, and even its pathogenesis is explained by similar hypothesis, that is, by a lesion of the vasomotor innervation of the vessels and by the action of a specific capillary toxin produced by the virus. The enumeration of the symptoms of this type of EHF would be a repetition of the symptomatology of the Far-Eastern type of fever which is the subject matter of this paper.

(Further data to be printed in the final edition)

5. The Bukovina hemorrhagic fever (67). This form of infectious hemorrhagic diathesis was detected in 1947 in Southwest Bukovina where it was found endemic in the woody hills of the Carpathian Mountains. It was described by KOLACHEV and KOSOVSKY, of Czernowitz, in 1949.

Here again, we have a sort of capillary toxicosis, caused by a virus, probably transmitted by *Ixodes ricinus* and other ticks to lumbermen and woodsmen. The symptoms are monotonous in all hemorrhagic fevers and acute onset, high temperature, hemorrhages, sometimes roseolar rash, flushed face, congested sclerae, bleeding from the mucous membranes, bradycardia, leukopenia, thrombopenia, and a series of unstable phenomena on the part of the somatic and vegetative nervous system.

The small epidemics occurred from June to August. The fever showed a saddle-back type. At autopsy, many organs showed small petechial hemorrhages. The findings were very similar to those in Crimean hemorrhagic fever, and even a virus neutralization test with the Omsk-virus gave positive results. The virus made cats and mice sick. As to the kidneys, they were not enlarged, and the albuminuria was not excessive (only in 13 o/oo of the cases, and it never exceeded 1 per mille except in 3 o/oo).





SOVIET UNION



Numbers are natural Equal Area Projection
at 1:10,000,000 1 inch = 642 statute miles

Statute Miles 0 100 200 300 400 500
Nautical Miles 0 100 200 300 400 500

CHAPTER VII

PATHOLOGY OF EPIDEMIC HEMORRHAGIC FEVER

There are a few Japanese autopsy reports. OZAWA and HAMAZAKI (4) published the autopsy findings of two cases in 1943. Much of the pathological and microscopic description of EHF in the Japanese literature was based upon the observations of Mr. ISIKAWA and Lt. TOKORO (1) in 40 autopsied cases.

HONZIN (1943) and associates described their findings in 80 autopsies, which they collected from 26 published Japanese articles (6). A few observations have also been made by autopsy of those monkeys which were used for the passage of the virus of the Sun-wu epidemic (1).

SATOH (1944) observed and examined 4 cadavers (38). HAMAZAKI (1946) described his findings in 8 autopsied cases (40). In 1949 KISIMOTO, of the Pathological Institute of Okayama Medical College, received material from 8 autopsies from an epidemic in Chiamussu (11).

Among the Russians, the pathological anatomy of EHF (or inf. NN) was chiefly described by MILASH and LEIBIN (25; 28). The paper of LEIBIN (1941) on 'hemorrhagic nephroso-nephritis' is the fundamental Russian description of the pathology of EHF (28).

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* *

In general, it may be stated that the so-called degenerative phenomena are present in varying degree in the organs, but the most characteristic and most important pathological change is the widespread non-inflammatory disorder of capillary circulation, manifested by a generalized dilatation of the small vessels, hyperemia, and small hemorrhages. Related to these changes there are also others in the smaller arteries and veins of organs (hystolysis, etc.) (1; 11), and development of perivascular infiltration in several organs (34), with the histiocytes predominating (26).

The chief sites of hemorrhages are the kidney, lung, gastrointestinal tract, anterior lobe of the pituitary, heart, liver, spleen, suprarenals (4), the lining of the renal pelvis, the brain cortex and the white substance, the pleura and the pericardium (26), the subcutis, and the muscles (26), occasionally with small necrotic foci and superficial ulcerations on the mucosal surfaces (28). Spontaneous ruptures and tears of tissues and organs are characteristic but rather infrequent (28).

The average pathologico-anatomical summary of the findings would ordinarily read as follows:

- 1) subendocardial hemorrhage in the wall of the right auricle of the heart,
- 2) advanced parenchymatous degenerations in both kidneys, with hemorrhages,
- 3) advanced fatty degeneration of the liver, with intra-parenchymal hemorrhages,
- 4) hemorrhages in the spleen and under its capsule,
- 5) hemorrhage in the anterior lobe of the pituitary,
- 6) marked hyperemia of the lung, with hemorrhages,
- 7) multiple small hemorrhages under the skin, mucous membranes, and serous linings all over the body (4) (25), under the pleura, the endocardium, the parietal peritoneum in the renal region (25),
- 8) submucous hemorrhage in the stomach,
- 9) hemorrhage into the dura mater, and the subarachnoid space (4) (11),
- 10) here and there free oozing of blood from the surfaces (25).

1. The general pathology of the blood vessels in EHF.

The changes in the blood vessels constitute the basic histological feature of EHF. In all cases which were examined histologically and in all organs of the body there was invariably a general, marked circulatory disturbance in the peripheral vessels, especially in the capillaries which showed *vasoparalytic* congestion, stasis, hemorrhage and extravasation of blood (5). Changes in the larger vessels were less manifest.

The blood vessels showed the following changes: 1) hypertrophy of the intimal cells, 2) proliferative capillaritis, 3) hypertrophy of the media, 4) fusion of the structure, especially in the media, with fibrinous swelling, loss of design, and formation of foamy cells, 5) a condition resembling polyarteritis nodosa, 6) perivascular inflammation and fibrosis, 7) perivascular edema and cellular infiltration, 8) vasoparalytic stasis, and hemorrhage. As to the polyarteritic aspect, one should not generalize upon this observation, which could be seen only in a few cases (5) (1).

Special staining showed that there was no lipoid infiltration in any vascular wall in any organ (28). In the capillaries of the mid-mediastinum HAMAZAKI found multiple emboli of myelocytes from the bone marrow (40).

2. Pathology of the hematopoietic system in EHF

a) Bone marrow.

The bone marrow changes vary from person to person, from bone to bone, and from portion to portion of the same marrow. Both red and yellow color could be seen in the marrow of the long bones (1). The marrow of the femur appeared rich in dark-red parenchyma (5). The redness of marrow is due to capillary dilatation, stasis, and hemorrhages. There is also an increase in hematopoietic function (1; 28), though TOKORO denies it (5).

The histological picture may show quantitative differences according to the site of examination. There can be a) a lipoid, b) a hemolipoid, c) a hemocellular, and 4) a cellular marrow distinguished. The majority of cases showed a hemolipoid marrow (5). Myeloid reaction at ectopical places has been suggested, but, if there was such an observation, at present its importance and specificity cannot be precisely stated (1).

b) Spleen.

The spleen is usually (55 o/o) slightly enlarged. It is not of a very soft consistency (5). There is, however, congestion, and extravasation of blood in spots, or diffusely, so that in extreme cases one could talk of a spleen of EHF (5).

In general, the spleen shows 4 types of changes: 1) hemorrhagic spleen, or splenic hyperemia; 2) splenitis proliferativa, not accompanied by splenomegaly; 3) splenitis exudativa, without splenomegaly (5); and 4) degeneration and necrosis of the lymph follicles (6).

The reticuloendothelial cells of the sinuses show varying degrees of proliferation from slight to moderate (1). Sometimes the sinusoids become invisible (4; 5), but mostly, they are blood-filled, and congested (5). There is proliferation of reticular fibers, proliferation of large monocytes and endothelial cells of the small capillaries and of the sinuses (6).

The lymphoid follicles show some atrophy (1; 26), sometimes even complete disappearance (4; 11; 26). There is no follicular hemorrhage (5).

The vessels of trabeculae, folliculi, and pulp are dilated, congested, and show diapedesis of red cells. The follicular arterioles and the pulp show edematous swelling (5), even hyaline degeneration, though this change was probably not specific (28). There was much cell infiltration under the endothelium of trabecular veins (1). In the pulpal small vessels small groups of neutrophil and eosinophil myelocytes were seen (28). Small pools of extravasated blood were observed all over the spleen (1), with scattered necrotic foci (5).

The cells in the pulpal reticulum are of various character: sometimes groups of eosinophils, or very rarely basophilic megakaryocytes (1). There were also independent, greatly swollen histiocytes, showing phagocytosis of blood (4). Though there were focal groups of eosinophilic leukocytes, young myeloblasts, and eosinophilic myelocytes, one should not call this a myeloid metaplasia (5).

Rarely, there is fibrosis and sclerosis (1). Others noticed colloid degeneration of the reticulum (5), but no fibrosis. HONZIN also found sclerosis (6) and considered these changes specific.

c) Lymphnodes.

The lymphnodes are more or less enlarged, congested, but not markedly prominent (1; 5; 28). The cervical and mesenteric lymphnodes were sometimes slightly swollen (6), hyperplastic (28).

The tonsil may be slightly enlarged, with occasional superficial hemorrhages (5). The lymphoid follicles of the gastrointestinal mucosa show occasional hypertrophy (5).

Under the microscope, the lymphnodes exhibit vascular dilatation, hyperemia, and small hemorrhages (1).

3. The pathology of the heart in EHF.

In general the heart may show the following changes: 1) hydrops, 2) edematous atrophy, 3) rupture of the myocardium, 4) parenchymatous degeneration, 5) hyaline, waxy or amyloid degeneration (the waxy degeneration is doubted by HONZIN; 6), also 6) fibrosis; 7) hemorrhagic necrosis, and 8) fatty or pigment deposit (5; 6).

The heart is flabby (25; 28). The myocardium is grayish-brown and easily torn (28).

There is marked dilatation, congestion, and diapedetic hemorrhage from the blood vessels of the heart. The hemorrhage is especially diffuse and marked on the endocardium of the right auricle of the heart (1; 11). There are also a few hemorrhagic spots in the myocardium (2), and most vessels are congested (2).

Less frequently, there is hemorrhage in the left ventricle, and the right ventricle also (5). The hemorrhage into the right auricle is explained by Japanese authors thus: the auricle becomes the center of a vacuum action which develops when the peripheral vessels of the entire body are suddenly and widely paralysed (5).

The stroma, especially in the papillary muscle and in the subepicardial portions of the heart (5), is edematous (28), loosened, especially around the blood vessels. There is noticeable fibrosis, infiltrative foci of histio-monocytes, endothelial cells, lymphocytes, etc. The histiocytes are basophilic. The circumscribed foci are around the adventitia of small precapillary blood vessels, and they appear sometimes as if they were small nodular granulomata (1; 26).

In addition, there is also a more diffuse type of infiltration in the stroma which gives the appearance of what was sometimes called a myocarditis of the stroma (1; 5). Out of 54 autopsies 7 cases plainly showed such nodules, 9 had them in less manifest form, and in another 15 cases the presence of the nodules could be detected after some search (6). Occasionally the heart resembled the heart of diphtheria with similar myocarditic granulations (11).

The endocardium shows slight proliferation of cells, with edematous changes in the connective tissue in many cases (1).

There were many hemorrhagic spots along the coronary arteries (6). The branches of the coronary in the myocardium show occasional disintegration of the vascular wall, swelling with blood plasma, loosening of structural design, proliferation of the connective tissue in the adventitia, and the presence of histiocytes in groups (as mentioned above). There is excessive sloughing of the endothelium, and the histiocytes may fill the lumen of the vessel (1).

The frequency of pathological changes was noted by the HONZIN group (6) as follows: a) parenchymal degeneration of the myocardium in 100 o/o, b) loss of structure in myocardial fibers in 100 o/o, c) fatty degeneration in some cases, d) vacuolar degeneration occasionally, e) partial hyaline degeneration in 25 o/o, f) disintegration in a few cases, g) brown pigmentation in the majority, and h) rupture in 50 o/o of the cases.

4. The pathology of the digestive system.

There are multiple hemorrhages under the mucosa of the stomach and intestines (25). Sometimes the entire intestinal tube, especially the lower part of the small intestine, is deep red, slightly swollen, resembling the cut surface of a pomegranate (6). The lumen may contain fluid blood in a few instances (25).

On the peritoneal surface of the intestines there is increased exudation, sometimes leading to ascites, edema of the mesentery, and stickiness of the serosa, with a few threads of fibrine (6; 28). The stomach is sometimes covered with multiple small ulcers which are coated with pseudomembranes (6).

Microscopy shows edema in the smooth muscles of the gastrointestinal tract, with atrophy (5), various degrees of hemorrhage in different layers of the intestine (6), especially in the mucosa and submucosa, accompanied by edematous swelling, and diapedesis of leukocytes.

Among the complications are catarrhal inflammation, proliferation of the solitary lymph-follicles, sometimes with necrosis of their germinal centers (6).

a) The liver of EHF.

The liver may be slightly swollen, with a slightly rounded anterior margin (28), and with an increase in weight up to 1800 or 2000 grams (28; 6). Its color is not jaundiced (6), except for an occasional grayish-yellow tinge (6). Out of 8 autopsies of KISIMOTO, only two cadavers showed jaundice (11). The cut surface of the liver may show a 'nutmeg' appearance (25; 28).

The general findings are 1) atrophy (sometimes widespread; 11) necrosis and degeneration of the liver parenchyma, 2) proliferation of the stellate cells in the capillaries, 3) hemorrhages (5). These changes were seen in 70% of the cases of the 1938-39 epidemics (6) which came to autopsy.

The liver cells, especially near the capsule, show granular and hydropic degeneration, with atrophy on one hand, and compensatory hyperplasia on the other hand. The lobular parenchyma shows scattered foci of necrosis, and larger, granuloma-like cell-groups (1; 26). Other workers speak of a slight regressive degeneration of the liver cells (2; 5).

Sometimes there are signs of pericapillary edema, with adjacent regressive changes in the parenchyma (1; 4). Occasionally,

the cytoplasm of the liver cells looks foamy (4). In the stroma there is not much change (2).

OZAWA stated that the stellate cells did not proliferate. Others saw that proliferation of the r e t i c u l o e n d o t h e l i a l cells was not rare. These cells may also show degeneration (1). Such degeneration is sometimes relatively greater than the parenchymal degenerative changes. Many of the reticuloendothelial cells may have pyknotic or atrophic nuclei, or their nucleus may be lacking (2; 4). There were also multinuclear giant-cells formed from the stellate cells, and their nuclei contained some i n c l u s i o n bodies of ca 2 microns size (4; 35).

The liver capsule is often infiltrated with lymphocytes and histiocytes (1;5). The vessels in general show dilatation, especially the liver capillaries, with congestion and hemorrhages (1; 5). One observer noted that there were large protein floccules under the endothelium of liver capillaries which stained pale red (4).

The b i l l i a r y t r a c t showed no visible changes (28).

The frequency of pathological changes in the liver was noted by HONZIN (6) as follows: 1) hemorrhagic and necrotic foci in 70°/o of cases; 2) turbidity of cells in 100°/o; 3) atrophy in many; 4) diffuse fatty degeneration in 90°/o; 5) brown degeneration in 60°/o; 6) hyperemia in 100°/o; 7) edema in many.

The capillaries of the liver contained lymphocytes, occasional (10°/o) polynuclears, eosinophil myelocytes (6). The proliferation, migration and degeneration of stellate cells was observed in many cases (6).

5. The pathology of the endocrine glands.

a) Thymus.

There was slight change observed in the fatty tissue or in the parenchyma, with exceptional hypertrophy (1), which is mostly a pseudo-hypertrophy. Passive hyperemia, and fatty infiltration of the thymus islets was also observed occasionally (5).

b) Thyroid.

In about 22.4°/o of the cases the thyroid is slightly enlarged, congested, with hemorrhages in its interstitium (26; 28; 39). In other instances it is diminished in volume, but the vessels are always congested (26).

c) Testis.

The testis shows congestion of the blood vessels in its interstitium (39). (I could not find any reference to ovaries).

d) Pancreas.

The pancreas of EHF is slightly smaller, and at times softer in consistency (28). It shows interstitial hyperemia, and occasional congestion in the Langerhans islets (29; 39). When there is retroperitoneal hemorrhage, the blood will also be found around and in the peripancreatic tissues (28).

One may also find focal necrosis, with blood pigment and macrophages in the centers of necrotic foci (28). In the interstitial stroma, especially along the excretory duct and around the blood vessels, there is some inflammatory (?) reaction in the form of infiltration composed of histiocytes, lymphoid elements, and polynuclears (28).

e) Suprarenal gland.

There is hemorrhage in the fasciculate zone of the suprarenal cortex (5). The cortex also shows: 1) degenerative atrophy and hydrops of glandular cells; 2) detachment and necrosis of cells due to pericapillary edema; 3) diminution or complete disappearance of lipoid substance (26); 4) cellular infiltration; 5) proliferative endotheliosis in the capillaries; 6) vasoparalytic stasis of blood; 7) hemorrhage and hemorrhagic necrosis (5; 25; 40; 28).

f) The pituitary and the infundibulum.

The pituitary gland of EHF is very characteristic in appearance. The gland may be increased in weight up to 2 gn (39).

In the anterior lobe there is dilatation, congestion and hemorrhages (24) in the capillaries. The cells may not show any specific change (1), though the chief cells are generally diminished in number (4; 40).

There is focal necrosis in the anterior lobe, and in a few cases the entire gland may become necrotic (5). The focal necrosis is the result of focal hemorrhages, at least to some extent. The cytoplasm of the eosinophilic cells is enlarged, and some of the cells are fused together, with some indistinct granulation contained in the plasma (4; 40).

In the middle lobe there seems to be no change (1), except congestion, hemorrhage and necrosis in the few cases when the infundibulum was also hemorrhagic (28).

IKEDA and associates (1944) suggest that EHF is characterized by hemorrhage in the pituitary and its neighborhood. In about 70% of the cases it develops quickly, and ends in necrosis (10). Since the pituitary controls many other endocrine glands, various functional disorders result. Similar findings were reported by the Russian workers in all cases of the disease which they called 'infectious nephroso-nephritis' (26).

In a series of 8 autopsies of KISIMOTO the pituitary hemorrhage occurred in 6 cases (11). Four of them showed also necrosis.

In the neurohypophysis small (15-20 micr.) granular balloons could be found in special cases. These balloons stained in violet color with hematoxylin (28).

Hemorrhages are also found in the infundibulum and the peripituitary tissue (28), the hypothalamic region, especially at the tubero-infundibular portion (28).

As a matter of curiosity it should be added that hemorrhages into the pituitary were rarely mentioned in the semi-old pathological literature. ZAJEVLOSHIN (1929; 70) described one case, and referred to a few other cases which occurred in erythremia, sepsis, typhoid, miliary tbc, and thyrotoxicosis.

6. The pathology of the respiratory apparatus.

(To be printed in the final edition)

7. The pathology of the skin and the eyeball.

The microscopical study of the skin shows dilatation and congestion of the capillaries, with hemorrhages into the corium, and pericapillary cellular infiltration in the papillae (1; 28; 37), with histiocytes, and proliferation of fibroblasts (5). There is also swelling of the endothelium of papillary vessels (28).

In the eyeball one finds hemorrhage into the ciliary body (5), passive hyperemia of the uvea (5), and the other clinical symptoms described before.

8. The pathology of the nervous system.

In all cases of EHF there is congestion, dilatation of vessels, and sometimes hemorrhages in the meninges and in the brain substance, sometimes with subdural and subarachnoidal hemorrhages (1; 25; 28) which may compress the brain.

Microscopy of the meninges shows the signs of the macroscopic changes: congestion, dilatation of vessels, and small hemorrhages (1). There is marked infiltration of lymphocytes and histiocytes in the p i a m a t e r (1; 6), with proliferation of endothelial cells (28). At the sites of pial hemorrhages the infiltrations also contain macrophages filled with blood pigment granules (28).

a) The brain.

The intracerebral capillaries are congested, dilated, and the brain substance shows hemorrhages (1; 2; 6) which may be small and large. Occasionally there are large hemorrhages in the diencephalon, and the hypothalamus (6) (See also under Pituitary, above). In the cortex the hemorrhages radiate from the lumen of vessels (25).

There was no case of evident malacia of the cerebral substance (6) and, clinically, the cerebral symptoms are comparatively few. In 9.1% of cases (2 cases) REZNIKOV reported exudative-proliferative hemorrhagic 'encephalitis', basing this diagnosis upon small hemorrhagic foci and some malacia (26) which he was able to observe.

There is no particular region (?) of the brain preferred by EHF (6).

In the layer of pyramidal cells in the c o r t e x, as well as in other layers of the cortex, and in the basal ganglia (6) there is degeneration of nerve cells to some extent, with neurophagia (in 56% of the cases), and tigrolysis (1). In certain parts of the brain (2) the nerve cells may completely disappear, leaving only glial cells behind (4). There are seen also 'Trabantenzenellen' (6), and, in 15 cases, foci of colloid cells (35). Degeneration of the pyramidal cells is seen occasionally (4), with some nuclear atrophy in 100% of the cases (6).

There is edema of the cerebral substance, especially around the capillaries (1), with marked swelling of the perivascular lymph spaces (2; 6), which might be filled with exudate, blood, and yellow ('colloid') granulocytes in 50% of the cases (6).

The endothelium of the congested capillaries shows cloudy swelling, desquamation, appearance of monocytes, disintegration of the walls of small vessels, slight hyaline degeneration, or other slight necrotic changes. This is in line with the pathology of the entire vascular system (6).

The gliosis is not especially marked (1). OZAWA noted a widespread proliferation of the glia in his second case (4), both in

(C.F.MAYER: Epidemic hemorrhagic fever)

the cortex and the cerebral white substance (11). Subependymal gliosis was strongly marked in the brain ventricles in LEIBIN's cases (28). In the ventricle one can also see perivascular round-cell infiltration in some cases (28).

Always in uremia, and sometimes also in other cases, there is slight dilatation of the lateral cerebral ventricles, with now and then small hemorrhagic spots on the ependyma (25; 26).

Hemorrhages also occur in the c e r e b e l l u m, the pons Varoli, etc.(28), and in the subependymal layer of the 3rd and 4th brain ventricles.

b) The spinal cord.

Congestion of the capillaries (2), spinal epidural bleeding (28), and congestion of the intraspinal capillaries, with edema, are observed (28). There is also degeneration of nerve cells in the horns of the gray matter, similar to that seen in the brain (2; 28). In one case, a spot of calcium deposit was noted (2) in the tissues.

c) Autonomic nervous system and the periphery.

Dystrophic disorders in the central and peripheral vegetative nervous system are considered typical of EHF (28). The c e r v i c a l sympathetic ganglia, especially the upper one, show congestion of the capillaries (26; 28), not rarely hemorrhages, and frequently signs of degeneration of the ganglion cells (28). Hemorrhages and degeneration of nerve cells is also observed in the peripheral nerves (28).

9. The kidney of EHF.

The renal changes of EHF are very similar to those mentioned in the Henoch type of hemorrhagic diathesis as the latter was described by KRJUKOV and AGAMALOV (69). The changes are, on the other hand, so characteristic that the Japanese workers referred to them as 'the kidney of epidemic hemorrhagic fever' (HONZIN; 6), while the Russians used the term 'infectious nephroso-nephritis' though the latter term is evidently incorrect (25).

The kidney is frequently enlarged, mottled or variegated and pasty. It may weigh almost twice its normal weight, up to 200-250-300 grams (1; 28). In a number of cases, however, it remains of normal volume (28). The characteristic kidney can be found only in persons who died after the fall of temperature, i.e., when the renal changes had already fully developed (6).

The capsule of the kidney is easily removed (6; 24 to 31). There may be hemorrhage under the capsule, in the surrounding fatty tissue, and on the surface of the renal cortex, due to rupture of the blood vessels (1; 24). The stellate veins are congested (28). Rupture of the kidney was comparatively uncommon (6; 28). In some cases there may be cortical ischemia (5).

The hemorrhage in the medullary portion of the kidney is so expressed that the Russians talk of an *apoplexy* of the kidney (APRIKOSOV; 24).

Sometimes the fibrous capsule may also rupture, and there will be hemorrhage into the retroperitoneal tissue, or into the peritoneal cavity (28). In a few cases the perirenal fatty tissue and the entire retroperitoneal cellular tissue is imbibed with blood and transudate which, in the peritoneal cavity might reach 1,000 ml (28).

The cut surface of the kidney shows pinkish-yellow, or ashy-yellow, pale cortex, cloudy swelling, against which the deep-scarlet or crimson, or dark-red ('cherry-red') medulla stands out in marked contrast, with clear boundary lines (1; 6; 24; 28).

One may find fibrin clots in the renal pelvis (6) which in the majority of cases shows petechial bleeding (6). From the cut surface of the pyramids blood may ooze freely (25; 28).

The mucosa of the urinary passages is hyperemic, frequently with extensive extravasation of blood (25). On experimental inoculation of monkeys this special aspect of the kidney could always be reduplicated (6).

The changes in the kidney are of 4 types according to Japanese workers: 1) glomerulonephrosis, 2) glomerulonephritis, 3) hemostasis and intraglomerular hemorrhage, 4) functional glomerular changes with little anatomical evidence of the disease. The most frequent is the first type. Though there is no typical diffuse nephritis, it is not unusual to see cellular infiltration to slight or moderate degree (5).

Russian workers say, however, that the microscopic examination of the kidney does not give basis for calling the renal changes by the term of nephritis, or nephroso-nephritis (28), though they call the disease so.

a) The renal cortex.

The *stroma* of the cortex may show 1) edema, 2) focal or diffuse cellular infiltration and proliferation, 3) slight proliferation of the connective tissue, and 4) changes in the blood vessels (5). Very rarely there are also small foci of necrosis (28).

The glomeruli exhibit a slight to moderate regressive change in their individual loops: - the walls are swollen, and the boundaries are indistinct. There may be fusion and atrophy (1) Nuclear degeneration is rare (4). Sometimes there is hydropic swelling or granular degeneration and disintegration of the epithelial cells of Bowman's capsule. In the lumen of the capsule the content is identical with that found in the tubuli (See below). A few glomeruli show proliferation of endothelium, almost of an inflammatory character, and excessive cellularity (1). It is however pointed out by the Russians that these changes are primarily non-inflammatory in nature (25).

b) The renal medulla.

The renal medulla shows most of the histological changes. The parenchyma is abundant with extremely congested capillaries-of the arteriolar rectae, and it is the site of severe hemorrhages. These hemorrhages may compress the tubules which then become atrophic. There are necrotic spots (5; 6; 24; 25). The necrosis is multiple in the pyramids, of pale yellow color, oval form or it may cause radial striation (28).

c) The renal tubuli.

The tubuli, especially the proximal convoluted tubuli (4), show hyaline-droplet degeneration, hydropic degeneration, or fatty degeneration. The epithelial cells tend to disintegrate and to show many changes from edematous swelling to granular deposits (1; 4; 5). These granules vary in size from 2 microns to 15 microns. The epithelial nuclei show degeneration, or lysis (4). The hyaline-droplet degeneration was especially characteristic in patients of the Japanese race (6).

In Henle's loops there are many hyaline casts (4). The epithelium on the side of these casts is slightly swollen, and shows granular hyaline-droplet degeneration (4). At some places, the epithelium is reddishly discolored from imbibition of hemoglobin (4).

The tubular lumen contains fibrinous, thread-like, granular or reticular protein masses (1), also a few red cells (4) in the form of casts (5). Sometimes, blood may fill all tubular lumina, and it may infiltrate the intertubular tissue (24). There is, however, no correlation between the severity of blood extravasation and the structural changes in the tubuli (25).

The usually flattened collecting tubules (4) near the papillary region contain hyaline casts. The changes often resemble nephrosis, especially glomerulonephrosis (1). The tubuli are often floating in extravasated blood (6).

The i n t e r t u b u l a r tissue is swollen and loosened, especially in the medullary portion. In some instances there is some proliferation of cells and cell-infiltration of the connective tissue (1). The stroma shows hemorrhages scattered all over the section (4).

The hemorrhage begins in the stroma of the medulla, and is soon followed by rupture of the tubules. It was pointed out that there is close relation between the granular and hyaline degeneration of the tubular epithelium and the hemorrhage (OZAWA; 4). This was, however, denied by others (25). (NOTE: Hyaline and granular degeneration of the tubular epithelium after renal hemorrhage was also observed in amphibians by OKAMOTO, and in man by HAMAZAKI) (4).

d) The renal vascular system.

The vascular system of the kidney shows an overall dilatation of the vessels, stasis, and hemorrhage. In the cortex, however, the capillary system shows such circulatory changes to a lesser degree than in the medulla, while the vascular plexuses of the cortex may also become veritable pools of blood (1).

In practically all cases there is a high degree of congestion in the glomerular capillaries (1), with endotheliosis in the afferent and efferent vessels (6).

The adventitia of larger vessels of the medullary layer is swollen, loosened into fibers, with some round-cell infiltration (25). The walls of arteries of middle caliber are thickened, and their muscular layer may appear homogenous, without cell nuclei (26).

There are small p e r i a r t e r i o l a r nodular or cuff-like accumulations of cells, mostly histiocytes (26). Often there is also periglomerular histiocytosis (6; 25), mixed with lymphoid elements (25; 34). These periarteriolar nodular changes are present in the small branches of the arcuate arteries to a greater extent than in, e.g., the branches of the coronary artery of the heart (1).

Though the Russians called the disease a kind of 'nephritis' they also recognized that the term was inaccurate because the clinical course and the renal pathology have many peculiarities which cannot be seen in 'nephritis' (25). Since the renal changes develop, or begin to develop during the febrile period of the infection, the renal process is rather an 'intrainfectious' than a postinfectious pathological process (25). There is no increase in the blood pressure, no subcutaneous edema, no signs of left ventricular failure, no edema of the lung, no angiospastic encephalopathy with eclamptic seizures (25).

CHAPTER VIII

PATHOGENESIS OF EPIDEMIC HEMORRHAGIC FEVER

The pathogenesis was described to some extent by KITANO and others (KIKUTI, NAGAYAMA, KASAHARA, ISIKAWA, SAKUYAMA, ASAHINA, and KANAZAWA) at a meeting in March and April of 1943 (1). The histopathological features of the study were made by TOKORO (5), and a number of Russian workers.

1. Portal of entry of EHF.

Experiments with the transmission of EHF from one monkey to another showed that while it is possible to transfer the infective virus by means of an injection of virus-containing blood into another blood-stream, there is no reaction to any other way of introducing the virus into experimental animals. Notably, the percutaneous, intraocular, and intranasal inoculations failed (1).

It is still doubtful whether the portal of entry in human infections is through the skin. There is no visible puncture of the skin which may be considered the bite of the Laelaps mite. It is, therefore, supposed that the virus is introduced by a painless bite of the mite (1). The further clarification of this problem will depend partly upon the further study of the feeding habits of Laelaps. It is uncertain at present whether the Laelaps mite is a blood-sucking parasite at all (1). (See VITZTHUM's views on p. 23).

It may be assumed that the virus enters the human body from the salivary glands of Laelaps at the time when the mite punctures the skin for sucking (1). Could liquid feces, or the juice of the crushed mite also penetrate the skin, and thereby inoculate the virus? (1).

2. The primary tissue reaction in EHF.

The clinical aspect of EHF may already be sufficient to suggest that the pathogenic agent is attracted by the vegetative nervous system (26). (NOTE: Modern virologists in Russia, such as CHUMAKOV, will object to any classification of viruses on the basis of so-called tropisms, calling one neurotropic, another viscerotropic, etc. The virus enters the blood-stream by the bite of an arthropod, and it produces a disease of the entire body; 79)

The nature of the hemorrhagic diathesis in EHF is not clear. Though there is a resemblance to the purpura of thrombopneic and/or vascular origin, the disease as a whole is different from any other known hemorrhagic disease. It is assumed that it is but a 'symptomatic' type of purpura in view of the existing vascular changes (1).

ISIBASI (1944), while accepting the resemblance to the Schönlein-Henoch disease as far as the origin of the hemorrhage is concerned, suggests that in EHF the hemorrhagic diathesis is accompanied by 'exudative' inflammation(11).

KISIMOTO (1949), however, regards the disease as of a non-inflammatory nature, and explains the finding of local, small round-cell infiltrations as secondary reactions to the hemorrhage (11). The disorder of the capillary circulation is considered of a vasoparalytic nature (1). The poison of the virus is a sort of capillary toxin (ISIBASI; 37; 33).

The disease is caused by an extremely virulent virus which multiplies in a very short period of time and produces the poison that is of a very general effect. The virus also invades the organs in the body successively (liver, kidney, heart, endocrine glands, cerebral centers), causing all kinds of functional disturbances (1).

The basic pathology of EHF is capillary congestion, stasis and vasodilatation. Where there is abnormal vasodilatation and stasis, hemorrhage may be expected(5). The circulatory disorder varies in intensity in each case. Even in the same case, it may differ according to the acid-base equilibrium status of the viscera.

The vascular and circulatory disorder will bring on some parenchymal disorder which may be either diffuse, as seen in the kidney, or circumscribed, as observed in the necrotic foci of the liver, and in the anterior pituitary (5).

Another sequela of the circulatory disorder is visceral edema. It is found to be widespread. The mechanism of this edema is, however, a controversial matter. (E. g., should it be considered a manifestation of a serous inflammation of the parenchyma, etc.) (5).

3. The histopathogenesis of EHF.

The virus of EHF does not act, however, upon the viscera alone but also upon the nerves (11). All morphological studies point to the capillarotropic character of the virus. For this

The first of these is the fact that the
government has been unable to
obtain the necessary funds to
carry out its policy.

The second is the fact that the
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The third is the fact that the
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reason the disease could be called *capillary toxico-sis*, a very comprehensive term, one of long standing, completely devoid of any etiological denotation since the introduction of this histopathogenetic idea by FRANK and GLANZMANN.

The following is a hypothesis of the pathogenesis of EHF.

The virus multiplies in the capillaries. It may attack a) either the vasomotor nerves, b) or the endothelium of the blood vessels, c) or both. There is some histological evidence that the attack is only by one of the assumed methods, i. e., there is a primary *vasoparalysis* which brings on congestion, stasis and hemorrhage, with degeneration of the vascular wall, pericapillary edema, and visceral swelling (TOKORO; 5). The small necrotic foci in the tissues are probably on the same order of development as the nodules in rickettsial fevers (5). In 1949, KISIMOTO failed to observe the changes in the vascular endothelium (11).

The Russians (LEIBIN, etc.) also concluded that the essential feature of the disease (of their hemorrhagic nephroso-nephritis) was the change in the circulation which occurs in all organs and tissues, and makes *hemorrhagic diathesis* the fundamental feature of the disease (28).

They also arrived at the hypothesis that the dystrophic changes in the small vessels and capillaries were caused very likely so that the infective agent acts either directly upon the vascular wall or upon the vegetative nervous system which then would create the vasomotor disturbances (28).

LEIBIN thought that, though the histopathogenetic problem cannot be solved without experimentation, the analysis of the clinical and pathomorphological data speaks for a primary affection of the *vasomotor nerves* (28).

The *hemorrhage* results from vasoparalytic congestion and circulatory stasis. It is a sort of *diapedesis* of blood, though there is no doubt that the vascular wall is also in disintegration (5; 28). The organic structural changes are, however, not the cause of hemorrhages. The hemorrhagic tendency varies individually: - some bleed more, some bleed less (5). Against this hypothesis, KISIMOTO considered that, at least in the liver, the necrotic foci are the primary, and the hemorrhage is the result of parenchymal necrosis (11) (*Quod erit demonstrandum!*)

The hemorrhages are limited to certain zones in the organs. Such *zonal hemorrhages* are seen: 1) in the kidney, where it is limited to the external segments of the medulla, and to the outward parts of the cortex, 2) in the liver, near the outer

part of the parenchyma, under the perihepatic capsule, 3) in the heart, chiefly to the right auricle, subendocardially, 4) in the suprarenal, to the fasciculate zone of the cortex, 5) in the gastrointestinal tract, to the top layer of the mucosa and submucosa, 6) in the eyeball, to the ciliary body, etc. (5). This zonal arrangement of hemorrhages is perhaps due to structural and functional peculiarities of the organs (e. g., structural in the kidney, functional in the heart) (5).

The changes in the pituitary and the diencephalon also suggest that the infection of EHF may be a primary disorder of the pituitary-diencephalic system (IKEDA; 10), akin to other pathological phenomena which would result from lesions of the brainstem (11). The possibility of a diencephalosis has been also stressed by the Russian workers (28).

4. The histopathogenesis of special symptoms in EHF.

The so-called renal syndrome has been known to be the standard feature of FRANK's hemorrhagic capillary toxicosis (68). With its peculiar anatomical structure and highly complicated function the kidney offers a 'locus minoris resistentiae' (REZNIKOV; 26).

Owing, however, to the many peculiarities of renal histopathology, the interpretation of renal changes is perhaps the most problematic and the most difficult in EHF since the clinical symptoms and the structural changes are almost unreconcilable with our long-established categories of renal disease.

The renal lesion starts its development during the febrile period; hence, the glomerular-changes could not be called a post-infectious glomerulonephritis. The clinical symptoms of an acute allergic diffuse glomerulonephritis are also completely absent (25). HATAZAKI, however, believes that proteinuria is the result of true glomerulonephritis, and of the degeneration of tubular epithelium rather than the result of renal hemorrhage (35).

The absence of edema, inspite of the almost complete anuria could be explained by the great loss of fluid, and loss of chlorides which results from vomiting. Another factor in the lack of edema is the absence of heart failure and of that vascular factor which is usually detectable in ordinary cases of acute diffuse glomerulonephritis. Apparently, the increased permeability of the vascular wall which is manifest in EHF is not sufficient in itself to cause subcutaneous edema (25).

The lipoido-nephrotic component which is found in allergic diffuse nephritis is also missing from the cases of EHF (25). ROTENBURG suggests that the clinical picture is extremely close to

that of toxic necronephrosis (25). Even the hyposthenuria that occurs in the convalescent period, and the corresponding severe alterations in the tubular epithelium which require a prolonged reparative period are analogous with the findings in necronephrosis (25). The similarity is further increased by the absence of a chronic renal disease in both ailments (i. e., EHF and necronephrosis) (25).

A chloroprive azotemia usually occurs in other infections, even in the absence of marked renal changes. It is partly due to marked destruction of the body proteins.

The stubborn vomiting develops very likely as a result of meningeal and cerebral lesions. The persistent vomiting then adds to the increase of chloropenia in the body. Chloropenia will promote, on the other hand, azotemia and contributes to the development of uremic syndrome.

The apparent erythrocytosis and the high Hb values in some cases are the apparent results of vomiting (25). In other cases an anemia may develop progressively owing to the azotemic uremia (25).

It was also remarked, by MAEKAWA, that EHF has some similarity to the "A T E R H O U S E - F R I D E R I C H S E N" syndrome, and he suggested that the chief feature of the newly detected epidemic fever might be anergic septicemia which is due to a primary insufficiency of the suprarenal gland (43).

CHAPTER IX

ETIOLOGY OF EPIDEMIC HEMORRHAGIC FEVER

IBUKI in 1938 talked of a strange form of scarlet fever. In 1939, -ISII felt that the 'new' disease was caused by an unknown agent. In 1943 KASAHARA found that the culture of the patient's blood, feces, urine, cerebrospinal fluid, sputum, and of the material taken from various viscera remained sterile under all possible conditions and on various-culture media. Neither bacteria, nor protozoa were found (3).

He also stained blood smears and visceral smears for protozoa, etc., but could not find any organism, except some Theileria-like bodies (3). In the same year it was discovered that the virus was carried by a mite, and in 1944 the Japanese literature referred to the disease as the first whose virus is carried by a mite (1).

Among the Russians there were many (TARASOV, TERSKIH, SHUBLADZE, KORSHINOVA, CHURILOV, etc.) who performed various bacteriological and virological studies, and animal experimentations for the determination of the pathogenic agent (25).

In spite of his unsuccessful experiments to isolate the specific agent of epidemic hemorrhagic fever in 1940, ROTENBURG concludes that it is a special nosological entity of infectious character (25).

1. The bacterial origin of EHF.

(To be printed in the final edition)

2. Early leptospiral theory of EHF.

(To be printed in the final edition)

3. The rickettsial theory of EHF.

Maj. Gen. ISII mentioned in 1940, after the study of the Sunwu epidemic of EHF in 1939, that the virus of EHF is composed of a filtrable and an unfiltrable portion, the latter being a sort of Rickettsia or Bartonella (1; 11).

This theory was further promoted in 1943. But, against the rickettsial origin of EHF it was pointed out that a) the type of the fever was different, b) the Weil-Felix test was negative, and c) the animal inoculations did not prove the presence of rickettsial bodies (KASAHARA; 3).

The rickettsial theory was further suggested and asserted by Naosuko HAYASI (8; 9) of the Tutugamusi Research Institute in Kurozyó (near Nagaoka-si). In 1948 he reiterated his belief.

(Further data to be printed in the final edition)

4. The theilerial origin of EHF.

Theileria as a cause of EHF was considered by Masazi KITANO and his associates. The first attempts at filtration did not exclude such a possibility. However, since the pathogenic agent

(C.F.MAYER: Epidemic hemorrhagic fever)

passed through L₅ and L₆ Chamberland filters, and through EK Seitz filter, Theileria was not further considered (1; 3).

(Further data to be printed in the final edition)

5. The virus of epidemic hemorrhagic fever.

In 1939, ISIKAWA and KASAHARA believed that the Sun-wu epidemic of EHF was a kind of v i r o s i s (3; 6). Viral origin of the disease was also mentioned by ISII and his assistants at the March 1940 meeting of the Japanese Army Medical Association. They suggested the existence of two viruses: 1) one filtrable and 2) one un-filtrable, the latter one resembling Rickettsia or Bartonella (1).

In and after 1943 the virus origin of EHF was generally accepted by the Japanese doctors (1; 35). It was said that the pathogenic agent was a f i l t r a b l e virus. By its pathogenicity and general properties the virus was ascribed to the v i s c e r o t r o p i c viruses by Japanese scholars.

Among the Russians the viral origin of their 'hemorrhagic nephroso-nephritis' of the Far-East was suspected as soon as the VIEM expedition reached the Primorskaya in 1940 (SMORODINCEV; 30).

a) Attempted isolation of the virus.

Since November 1942, the virus of EHF was kept alive by animal passage from monkey to monkey (1). It was also possible to recover the virus from Iaelaps jettmari (Nov., 1942; 3).

The virus can be preserved in infected blood when such blood is mixed with citric acid or with citrated saline to prevent its coagulation, and then kept at near freezing temperatures (1). It is also successfully preserved in dry-frozen spleen kept at a temperature as low as -70°C.

b) The distribution of the virus in the body.

The virus was considered v i s c e r o t r o p i c. Observations of neuronophagy, and other degenerative changes in the cerebrospinal neurons and the subsequent gliosis show, however, that the virus of EHF is also n e u r o t r o p i c, or should we say, p a n t r o p i c or comprehensive in nature (11).

It was found that there is some dissociation between the time when the virus is the most concentrated in the blood and the time when the patient is physiopathologically the sickest. The virulence of the patient's blood is the strongest during the initial stage of the disease up to the time of highest fever. After the

drop in temperature, especially when it returns to normal, the blood has no more infective power (1; 3).

The virus is found both in the cellular and the fluid elements of the blood, i.e., in the erythrocytes, leukocytes, thrombocytes, plasma and serum (1; 3). It is also present at some time in the various organs (3).

After the crisis in temperature, the concentration of virus must be very small in the organs which anatomo-pathologically are so characteristic of EHF, i.e., primarily in the 'epidemic hemorrhagic fever kidney'. Hence, such organs are unsuitable sources for the isolation of virus; at the time of autopsy, they are already in a state of dissolution, without much virulence (1). For visceral emulsions one has to secure an organ from the initial stage of the disease (3).

c) Filtrability and size of the virus of EHF.

Attempts at filtration of the pathogenic agent began in 1939 (ISII; 1). The virus was thought first to have two different components, filtrable and unfiltrable. The material used for filtration experiments was hirudinized blood plasma, citrated blood plasma, and emulsions prepared from various viscera (liver, spleen, kidney) (1).

In April 1943, KITANO found that the virus passed through the L₂ and L₃ Chamberland filters. First he thought that it might be a filtrable form of Theileria. His later experiments, however, showed that the virus of EHF also passed through the L₅, L₆ and L₉ Chamberland filters, and through the EK Seitz filter.

He made seven experiments of filtration, and though two of them gave negative results, there was little doubt left that the pathogenic agent of EHF was a f i l t r a b l e v i r u s (1;3).

d) The elementary and inclusion bodies in EHF.

On histological preparations of material taken from infected monkeys during the first, febrile stage of EHF, small inclusion-like bodies are seen in the liver cells and the pulpa cells of the spleen. These inclusion bodies are i n t r a n u c l e a r.

The basichromatin of the nuclei which shows such bodies is condensed at the margin of the nuclear membrane, and 1 or 2 roundish or ovoid, acidophilic, small bodies are seen in the nucleus. E l e m e n t a r y b o d i e s are not seen. The significance of these findings is left open for discussion. It was thought in 1943, when these inclusion bodies were described by KASAHARA, that

even if they were not proved true inclusion bodies one should not exclude the possibility of such elements in EHF (3; 35).

In 1943 OZAWA saw also intraepithelial eosinophilic granules in many cells which filled the lumen of collecting tubules of the kidney. At some sections he also observed epithelial cells containing many small, 2-micron-large round hyalonoid bodies (4). He also observed i n t r a n u c l e a r inclusions in some giant cells of the liver which were formed by fusion of several reticulo-endothelial cells. These bodies were ovoid, 2 microns in size. In the nuclei of other stellate cells he found indistinct, eosinophilic bodies (4).

Further microscopic research is needed to decide whether the virus of EHF includes elementary bodies and inclusion bodies in its life cycle (KITANO; 1944). Some of the observed small bodies have also been thought to be developmental forms of Theileria or Rickettsia, at least by those who do not accept the viral origin of EHF. HAYASI in 1948 suggested calling this rickettsial organism Rickettsia laelaps manchuriae, n. sp. (9).

In 1949 KISIMOTO searched several liver preparations for these inclusion bodies. He rarely found acidophilic bodies in the nuclei of stellate cells, or in the liver cells proper. He doubted, however, that they were true inclusion bodies. They were indistinct, and the marginal condensation of the basichromatin was not sharp. Nevertheless, he held it possible that after several passages of the virus of EHF through successive sets of animals, the intranuclear inclusion bodies might develop (11).

To this it may be added that animal passage of a virus may sufficiently modify it as to make the virus able to produce intranuclear inclusion bodies. This happened, for instance, in the experiments with the virus of epidemic encephalitis (HATAZAKI; 1943).

e) Resistance of the virus of EHF.

The virus of EHF was found to be resistant to cold. The infected blood retains its virulence for six days when it is kept at 4°C, while at -3°C the virulence may last eight days (1).

Dry-freezing of the infected blood (to which citrated saline has been added) at -70°C, preserves the virulence of the virus for at least eight days, while in a dry-frozen spleen (at -70°C) the virus survives for 11 days (1). Another worker states that under such conditions the virus survives 81 days (3). Under similar treatment, protozoa and spirochaetae lose their virulence rapidly (3).

f). Cultivation of the virus of EHF.

No one has yet been able to cultivate the virus in any form. ROTENBURG inoculated various culture media with infective material, with negative results (25). (NOTE: The virus disappears from the blood after the febrile period.)

g) Transmission experiments.

On November 6, 1942, at the time of the Sun-wu epidemic of EHF, 40 field-mice (*Apodemus agrarius mantchuricus*) were caught by the Japanese Army, and 203 specimens of *Iaelaps jettmari* were made into a saline emulsion. This material was used for injection of monkeys in order to prove the vector role of the mite.

The emulsion was injected subcutaneously into the thighs of the monkeys. Nineteen days after the injection, the animals developed a fever of 39.4°C. Next day (on November 26), the blood of these sick monkeys was injected into another set of healthy monkeys. The second set also became ill with the same typical disease, i.e., with EHF, as proved by autopsies (1; 3).

In the second set, which was injected with blood taken at or during the fever, the disease appeared 12 days after the inoculation. It was introduced by fever which was followed by the typical proteinuria.

The host rodent, *Apodemus agrarius mantchuricus*, and the ordinary house mouse (*Mus musculus*) show no visible signs of the disease when they are injected with virus-containing blood (1). One *Apodemus* was inoculated with 0.5 ml infected blood, and kept under observation for 25 days, but there were no visible signs of sickness. One ml of the emulsion, prepared from the viscera (liver, spleen, kidney) of this animal, however, produced EHF in a monkey upon subcutaneous injection (3).

In another set of experiments the house mouse (*Mus musculus*) was infected with 0.5 ml of virus-containing blood by intravenous route. Nineteen days after the inoculation the animal was still healthy, without any visible effect of the inoculation. Then, the viscera (liver and kidney) of this animal were used to prepare an emulsion with 10 parts of Ringer solution. The visceral emulsion was injected into monkeys. Thirteen days after the subcutaneous inoculation of the emulsion the monkeys developed typical EHF (3).

Such animal experiments show that these rodents, i. e., *Apodemus agrarius manthcuricus*, and *Mus musculus*, are permanent reservoirs of the virus of EHF.

HALPERIN, of the Narkmozdrava Expedition to the Far-East, also made animal inoculations in 1939 but with negative results (33). His experiments chiefly ruled out the bacterial, leptospiral and other protozoal theories of the origin of EHF.

Moreover, he used guinea pigs which he injected with blood taken at the first stage of infection. Blood when taken on the 10th day of sickness also gave negative inoculation results.

Other Russian workers also made animal experiments in order to determine the susceptibility of these animals to the disease. Albino mice, albino rats, rabbits, and *Macacus* monkeys were inoculated with blood, urine, spinal fluid, chest punctate of the patients who were still in the first stage of their sickness. Transmission experiments were also made with organ emulsions. None of the animal inoculations gave positive results to ROTENBURG and the Markmozdrava Expedition in 1938-39 (25).

The susceptibility of horses and cats to EHF has been mentioned before. The KASAHARA Research Group also gave experimental proof that the virus of EHF may cause a purpuric type of febrile disease in North-Manchurian horses (1).

CHAPTER X

IMMUNITY IN EPIDEMIC HEMORRHAGIC FEVER

1. Human immunity to EHF.

Japanese doctors assert that there is a very low incidence of EHF among native Manchurians (1). (Would this mean the presence of a natural immunity, or the development of antibodies after contracting the disease at early childhood?)

Little is known about the antibodies of EHF. Experiments with passive immunization, by means of convalescent serum, are still not convincing (CIGANKOV; 1941) (33).

Allergy in EHF was studied by IKEDA in 1946 (41). The skin test which he suggested was described on p. 45. Here are further details on his antigen and the test.

He prepared his antigen from liver, spleen, and kidneys taken from those who died of EHF. The tissue pieces were ground up in a mortar with the aid of corundum, then macerated under sterile conditions. The macerate was then diluted with saline or Ringer solution, or Tyrode solution, to ten times its original volume. Then, it was filtered through L₂ or L₃ Chamberland filters. Then, the filtrate was treated with phenol (0.4 o/o).

Through the Mantoux technique of tuberculin testing IKEDA injects 0.1 ml of his antigen intracutaneously into the outer side of the upper arm, or on the inner side of the forearm. The site of injection is kept under further observation. For control, 0.1 ml physiological saline is injected intracutaneously at a site not farther than 3-5 cm away from the antigen injection.

The test is read after 24 hours. There is usually a hyperemic area around the site of injection. This erythematous area is measured with a ruler. If the diameter of the area is one cm or below, the test is called negative. An area of hyperemia from 1.1 cm to 1.9 cm is read as 'one-plus'; one from 2.0 cm to 2.9 cm is 'two-plus', and so on.

In addition to the hyperemia there is usually some infiltration, swelling and occasional formation of bullae or vesicles.

On the reliability of the skin allergic test IKEDA states that the test will give positive results even for some time after the recovery from EHF (41). Whether there is some type of active immunity against a new infection with the virus of EHF remains to be seen.

2. Animal immunity to EHF.

None of the rodents in whom the virus of EHF was discovered dropped dead (1). (During a plague epidemic, rats would die from the disease).

Some of the Japanese physicians observed that at times of the human epidemics of EHF in Northeastern Manchuria the horses also were suffering from a strange febrile disease. The disease of the animals was looked upon as a mixture of equine influenza and infectious anemia, or just plain influenza and plain infectious anemia.

Some of the veterinarians diagnosed the disease of the horses as a) toxicosis caused by an unknown agent, b) endemic piroplasmosis, c) trypanosomosis, d) equine purpura, e) very severe case of malleus, or f) anthrax (1).

It is interesting to see that so many horses were sick with an unknown fever. KASAHARA, IKARI, SAKUYAMA, KATO, and OHNISI proved that the virus of EHF is pathogenic also for the horse and that it may cause a certain degree of fever in that animal (1).

The susceptibility of cats to EHF is mentioned on p. 17 of this paper.

3. Relation of EHF virus to other viruses.

It is suggested that the virus of EHF may have a close relationship with the viruses of dengue and of yellow fever (1).

ROTEBURG carried out virus neutralization tests by using organ emulsion from patients with EHF and the virus of seasonal encephalitis. His experiments remained negative (25).

KOLACHEV (67) and other Russian workers showed that there may be a very close kinship between the recently described various forms of EHF (See p. 49-50). Such relationship was proved at least for the Omsk and the Bukovina viruses. The sera of patients who suffered from the Bukovina type of EHF neutralized the virus of the Omsk virosis.

CHAPTER XI

PREVENTION OF EHF

Not knowing the exact nature of EHF, its mode of spread, its many possible reservoirs and vectors, the prevention of the disease must include such general measures as 1) control of the transmission of virus as far as possible, 2) extermination of the detected sources of infection, 3) blocking of the paths of infection, and 4) individual prophylactic measures (1).

1. Control of rodents.

The most effective measure in the prevention of EHF is the destruction of rodents and of their nests along the banks of the rivers, or wherever they are found.

Special attention should be paid to prevent the contamination of houses and other dwelling places. The rodents should be caught both inside and outside the house.

The control of rodents will take care also of the virus carrier mite, the *Laelaps* which does not easily leave its host.

2. Control of Laelaps mite.

Since the mite attaches itself to grass or hay, or that is what one supposes, it is necessary to exercise care in handling such material, at least in the known contaminated districts.

Another suggested method is to burn the vegetation and grasslands, the dry grass around the habitations, in the fall. This will achieve both the extermination of Laelaps and the exposure of the innumerable nests of rodents (13).

When a house is known to be contaminated the grass and hay used for bedding, etc. should be burnt, and the human clothing should be disinfected.

3. Personal measures.

Personal measures were tried out chiefly by the Japanese Army in Manchuria (1). They consist in special care in handling grass or hay, disinfection of clothing, etc. One should remember that during extermination of the rodents, a person may come in close proximity to the nests of the rodents. Around such nests the ground is full of mites and other arthropod parasites which may easily become attached to the clothing.

In its attempt to develop further effective means for personal protection the Japanese Army developed a) an oil prepared from the white birch tree which was supposed to be repellent to the mite; also b) a kind of protective shirt to prevent easy contamination with the mite. Other individual protective measures were being studied in 1944.

On the Russian side, it was recommended that those who attend horses should use special care in dealing with them (33). It was also recommended that such persons wear overalls, rubber gloves, and high boots while bathing the horses in the rivers. Thereafter, the people should undergo a thorough disinfection.

4. General measures.

In 1942 the Japanese Army established a quarantine service against EHF, but it did not prove effective in controlling the outbreaks (1). At such a station in Chientao, for instance, persons as well as the entire environment were subjected to systematic examination.

CHAPTER XII

TREATMENT OF EPIDEMIC HEMORRHAGIC FEVER

A patient suffering with EHF should be dealt with in exactly the same way as any other patient with an acute, non-contagious infectious disease. Among the Japanese, the patient was isolated in a hospital and subjected to all rules of disinfection. (1).

The majority of the Russian patients were hospitalized until the end of the fever, sometimes even during the second stage of the disease (25).

1. Specific treatment of EHF.

In 1940 the Russians recommended the use of convalescent serum, but the results of such experiments were not mentioned (25). In one instance, the patient was given 12 ml of convalescent serum on the 3rd day of sickness.

S'ORODINCEV recommended convalescent serum, and in 1941 CHURILOV believed that the early use of such serum might abort the further advancement of EHF. Such preventive and abortive effect of the convalescent serum has to be verified by clinical trials (29; 34).

Convalescent serum was also employed by the Japanese who generally reported good results from its use (1; 34). But even the blood transfusion from non-convalescent patients proved to be of good effect when used judiciously (in small amounts).

It has been stated that U. S. physicians are now engaged in developing a specific vaccine against EHF (15).

2. General management and medication.

For a sort of antidote against the toxin of the virus of EHF various neutralizing measures were used such as large amounts of fluid to be given at the early stage. The fluid may be in various amounts and of various quality (Ringer solution up to 2 quarts (25), or isotonic glucose solution, or saline with 5 o/o glucose solution).

For the protection of the liver and kidney one resorts to a) large doses of vitamin preparations, by injection or by mouth, especially ascorbic acid (29), b) injections of glucose-insulin, and c) alkalization of the body.

During the second stage of the disease the therapy should be directed a) against dehydration of the organism, and b) for re-chloruration of the body (25).

The symptomatic treatment includes a) medication for the support of the heart and circulation (digitalis, strophanthin, ouabain, adrenaline, strychnine at time of crisis, other cardiotonic, and diuretics), b) medication against the pain (sedatives, opiates) (25). It was, however, the experience of CHURILOV that nothing helps against singultus, and vomiting.

Russian physicians experimented with the so-called V i s h - n o v s k y type of nerve-blocking in order to alleviate lumbar pain, hiccup and vomiting. They had no success with such treatment (25).

The d i e t should be chiefly lacto-vegetable, with weak soups, fresh fruit juices, ice cream, etc. (1; 25).

The U. S. Army experimented with the use of a n t i b i o - t i c s in EHF, but according to official announcements, no one of these substances was of avail (15).

A Russian military surgeon (KOLACHEV; 61) brought up the question of evacuation and transportation of patients suffering from infectious hemorrhagic diathesis. His recommendation was that, since the disease is non-contagious, the patient may be removed to the field hospital. If bleeding would set in, however, he should be considered non-transportable, and his treatment should be carried out in the (Russian) hospital platoon, at least until the disappearance of the more threatening symptoms. If the bleeding recurs, the patient has to be transported in bed, and he should be kept under medical supervision during the transport (61).

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CONCLUSIONS AND FUTURE PROBLEMS

The survey of the available Russian and Japanese literature on EHF shows that there are many aspects of the disease that need further concentrated study and the cooperation of various kinds of professional people, such as physicians, zoologists, bacteriologists, virologists, etc., including those who coordinate the results of investigations to facilitate the progress of field workers.

Several points in the epidemiology of EHF are still questionable. At present, the role of Apodemus seems to be certain in the outbreaks of EHF, but there are indications that other rodents may also play active role in the spreading of the disease.

The habits of all possible reservoirs of the virus of EHF need further study. *Laelaps jettmari* may not be the only vector of the virus as suggested by some studies. It is still a question whether *Laelaps* is a bloodsucking mite. Its developmental cycle should also be studied in the field.

There are indications that the infection may do some damage in the renal function which will last longer than one would believe from the apparent mild course of illness. Clinical studies should be carried out, with careful follow-up studies, to determine the sequelae of infection.

Pathological research indicates that, though it is a general infection, EHF releases its fury upon the kidney and the pituitary gland. Further clinical studies are necessary to correlate the clinical symptoms, which are numerous, with the organic lesions.

Diagnostic difficulties remain until adequate biological tests are developed for the differentiation of EHF from other similar infections which may appear under the mask of hemorrhagic diathesis. The few attempts at developing such diagnostic tests should be carefully rechecked. Indeed, all data collected from the literature and assembled in this paper need confirmation by American physicians and naturalists at the clinics and laboratories.

The nature of the virus of EHF is still unknown, though its filtrability has been ascertained. It was never isolated, never cultivated, and its relation to other viruses needs further study. In view of the many infectious hemorrhagic epidemics in Soviet Russia, the relation of the Manchurian-Korean type of the virus to the pathogenic agents of these other fevers should be cleared up.

Among the possible animal reservoirs the importance of the horse and the cat has been suggested, but not yet finally proved. Study of equine infectious purpura and its relation to EHF is also an urgent problem. The observations of veterinarians should also include the diseases of other domestic animals during EHF epidemics.

Prevention has to be restricted chiefly to general sanitation, since the exact life habits of the animals which spread the disease are not known. It may be considered a problem whether the contaminated hay or grass could be salvaged by disinfection when large quantities should otherwise be destroyed for the destruction of mites.

The problem of personal prevention will remain unsolved while a suitable vaccine for active immunization is lacking. Neither can the present method of treatment be considered satisfactory, and further clinical studies are necessary to confirm the value of convalescent (or other kind of) serum in the treatment of EHF.

S U M M A R Y

A collective survey of the Russian and Japanese literature on epidemic hemorrhagic fever coordinates the various facts known on this infectious disease endemic in the Far-Eastern countries under Russian and Japanese rule. Called by many names, it has a history of about 15 years, and is the topic of current American research.

The history of research on epidemic hemorrhagic fever, the geographical distribution of the disease, its epidemiology, climatic and seasonal incidence, vectors and reservoirs are analyzed. There are chapters for the synthesis of data on the clinical course and symptomatology, the clinical pathology, diagnosis, pathological anatomy and histology, on the pathogenesis, etiology, and the nature of the virus, on the prevention and treatment of this Manchurian-Korean virus disease.

A final word is said about the problems of research awaiting further study. Several illustrations are attached to show the vectors, the geographical distribution, and clinical peculiarities of the disease.

Washington, D. C., 7 December, 1951.

Claudius F. Mayer, M. D.

LITERATURE

(Full annotated bibliography will
be printed in the final edition)

(KEY to the names of research
workers follows on next page)

KEY TO RESEARCH WORKERS
quoted by numbers

- | | |
|----------------------------------|---------------------------|
| 1 KITANO M. 1944 | 41 IKEDA N. 1946 |
| 2 SUZUKI K. 1943 | 42 ONO K. 1944 |
| 3 KISAHARA S. 1944 | 43 YEKAW M. 1943 |
| 4 OZAWA S. 1944 | 44 KITANO M. 1944 |
| 5 TOKORO Y. 1944 | 45 IBE T. 1938 |
| 6 HONZIN R. 1944 | *46 SVOYAKA S. 1939 |
| 7 URUMO K. -1943 | *47 HARA T. 1939 |
| 8 HAYASI N. 1943 | *48 SHIMIZAKI Y. 1940 |
| 9 " 1948 | 49 OGATA T. 1946 |
| 10 IKEDA K. 1944 | *50 " 1948 |
| 11 KISIMOTO M. 1949 | 51 OKAMOTO R. 1938 |
| 12 VITZTHUM H. 1930 | 52 KUBO H. 1938 |
| 13 TB MED: 216. 1946 | *53 MIURA U. -1940 |
| 14 HSIAO T.Y. 1946 | *54 TAMURA Y. 1940 |
| 15 J.A.M.A. 1951 | 55 OKAMOTO R. 1937 |
| 16 TERSKIN V.I. 1936 | 56 - |
| 17 " 1936 | 57 KASSIRSKY I.A. 1948 |
| 18 WASH. POST 1951 | 58 SIPOVSKY P.V. 1944 |
| 19 U.S. ARMY ARCTIC BR. 1945 | 59 SEMENOVSKAJA Z.V. 1950 |
| 20 EVENING STAR 1951 | 60 KLEIN J.S. 1951 |
| 21 " (Nov.8) 1951 | 61 KOLACHEV A.A. -1945 |
| 22 WASH. DAILY N. 1951 | 62 ABRIKOSOV A.I. 1950 |
| 23 DEUT. VER. ROT. KR. 1908 | 63 CHURIAKOV M.P. -1947 |
| 24 ABRIKOSOV A.I. 1950 | 64 PERFILJEW P.P. 1947 |
| 25 ROTENBURG S.S. 1940 | 65 DROBINSKY I.R. 1948 |
| 26 REZNIKOV A.I. 1940 | 66 " - 1948 |
| 27 DUMAEVSKY L.I. 1941 | 67 KOLACHEV A.A. 1949 |
| 28 LEIBIN L.A. 1941 | 68 SILVESTRE J. 1938 |
| 29 CHURILOV A.V. 1941 | 69 KRJUKOV A.N. 1940 |
| 30 " 1941 | 70 ZAJEVLOSHIN M.N. 1929 |
| 31 TERSKIN V.I. 1941 | 71 BELONOSCHKIN H. -1937 |
| 32 GALPERIN E.A. (HALPERIN) 1939 | 72 SOVERBY A. de C. -1923 |
| 33 CIGANKOV-G.M. 1941 | 73 HAYMAN R.W. -1941. |
| 34 KITANO H. 1944 | 74 JETTAR H.M. 1931-32 |
| 35 HAMAZAKI Y. 1944 | 75 SVIRIDENKO P.A. 1944 |
| 36 NOMURA H. -1944 | 76 JETTAR H.M. 1927-28 |
| 37 ISIBASE T. 1944 | 77 KTEGAN H.E. 1950 |
| 38 SATO T. 1944 | 78 SNAPPFR I. 1941 |
| 39 TAKAMI R.M. 1951 | 79 CHURIAKOV M.P. 1949 |
| 40 HAMAZAKI Y. 1946 | 80 ROBERTSON D S 1942 |

(items marked with * and numbers without names
have been omitted from the preliminary draft)

